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ENDOCRINOLOGY

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Guest Editorial

Born in Toronto, in 1926, Calvin Ezrin graduated as an M.D. at the University of Toronto in 1949 and became a Fellow of the Royal College of Physicians of Canada in 1954. His interest in endocrinology in general and in pituitary disorders in particular dates from the period of his training under the late Professor R. F. Farquharson, a teacher whose memory he treasures with gratitude and admiration. He has meanwhile published a large number of papers recording the fruits of his research in a wide variety of fields, including the cytophysiology of the anterior pituitary, the kinetics of thyroid-hormone transport, insulin resistance, and the effect of glucagon on intermediary metabolism.

Having attained consultant status only five years after graduating, and after winning several prizes and awards for his work, Dr. Ezrin was in 1965 appointed Assistant Professor in the Division of Neuropathology (Department of Pathology) at the University of Toronto. Despite his keen interest in research, he continues to keep in touch with general medicine in his capacity as a physician at Toronto General Hospital, and he also teaches physical diagnosis to medical students. While still a medical student himself, he managed to become a professional musician and, although upon graduating he abandoned this profession for the more noble one of medicine, music has always remained his favourite pastime.

It is instructive to list the various disciplines that are involved in the study and practice of endocrinology. Anatomy, physiology, biochemistry, physics, pharmacology, immunology, genetics, pathology, internal medicine, surgery, obstetrics, gynecology, paediatrics, psychiatry, public health and statistics are those that concern the medical student. The need for integration of our curriculum dealing with endocrinology was recognised nearly 20 years ago by a representative group of undergraduates who approached the dean with the suggestion that a course be given, relating all of these subjects as they applied to endocrine function and disease. It was rejected as being impractical. Since then the students have been taking out their frustration with the fragmented way endocrinology is being taught by periodically composing thoughtful, integrated reviews for presentation at AOA meetings or for their colleagues to read in the U. of T. Medical Journal. The authors of the articles contained in this issue, which are excellent examples of this type of work, should be commended for taking the time and trouble to bring the results of their reading, thinking and discussions to the attention of their confreres. I am sure they will agree that they have already been amply rewarded by the pleasure experienced in producing a respectable scholarly article.

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The Influence Of The Central Nervous System On The Pituitary Gland

A. D. Tepperman 6T8

The intimate relationship of the pituitary gland to the central nervous system is one which is necessary for the co-ordinated functioning of many of the body's essential processes. This paper will attempt to review the basis of the relationship of the central nervous system, and more especially the hypothalamus, to the pituitary gland, and to discuss the mechanisms by which this control is achieved.

In order to understand the physiology of this inter-relationship one must first review the significant anatomical relationships of the hypothalamic-pituitary complex.

The pituitary gland is composed of two parts: the anterior part or adenohypophysis derived from the ectoderm of Rathke's pouch of the stomodeum and the posterior part, or neurohypophysis derived from neural ectoderm of the ventral part of the forebrain.

The salient features of the anatomical relationship are these:

1. The adenohypophysis' blood supply is entirely from the long and short hypophysial portal vessels which are derived from the superior and inferior hypophysial arteries after the capillary beds are formed. The adenohypophysis receives no arterial blood, but is drained by veins which empty into the systemic circulation.

2. The axons of the cell bodies of the supraoptic and paraventricular nuclei of the hypothalamus terminate about a capillary network in the neurohypophysis which enters directly into the systemic circulation. The cell bodies from different nuclei also terminate about the capillary systems which drain into the long and short hypophysial portal vessels which supply the anterior pituitary.

MECHANISM OF CONTROL OF SECRETION OF THE PITUITARY GLAND

The following mechanism of pituitary control is generally accepted.

Neurohypophysis

The axons of the neurons in the hypothalamus which terminate in the neurohypophysis are neuro-secretors. These neurons produce polypeptide substances (hormones) which travel down the axon and are released in the nerve endings in the infundibular process. The flow in the axons is possibly due to pressure exerted by hormone synthesis in the perikaryon, or by the pulsation of the oligodendroglia cells. The stimulus for secretion is mediated by neural (reflex) or chemical receptors in the hypothalamus. Each of the hormones of the neurohypophysis will be discussed later, as will the control of their secretion.

Adenohypophysis

The hormones of the adenohypophysis are secreted in response to releasing factors produced in the hypothalamus. The releasing factors travel down the axons to reach the capillary plexi which precede the long and short hypophysial portal vessels. The releasing factors are thus carried to the adenohypophysis and presumably diffuse out to influence specific cell activity. The cells of the adenohypophysis produce secretions which in turn stimulate target glands to produce their appropriate hormones. These latter hormones (present in the systemic circulation) reach the hypothalamus and pituitary and there exert a negative feedback effect. There are individual variations of each of the specific hormones' regulatory mechanisms and these will be discussed later.

HYPOTHALAMIC REGULATION OF THE HORMONES OF THE NEUROHYPOPHYSIS

1. Vasopressin (ADH)

Vasopressin is produced in the supraoptic nucleus of the hypothalamus. This hormone is secreted in response to increased osmotic pressure of the intravascular compartment. The osmostat which regulates this secretion by constant sampling of the intravascular osmolarity is found in the hypothalamus and there is evidence which suggests that the supraoptic nucleus is also the site of the osmoreceptors. There is also a drinking center in the perifornical region of the hypothalamus which has an as yet undetermined relationship to control of extracellular fluid osmolarity. The vasopressin travels down the supraoptico-hypophysial tract to be released in the infundibular process. In high section of the hypophysial stalk, the axons of this tract atrophy and diabetes insipidus results.

2. Oxytocin

Oxytocin is produced in the paraventricular nucleus of the hypothalamus and travels down the supraoptico-hypophysial tract to be released in the infundibular process, and there is picked up by capillaries which enter directly into the systemic circulation. Oxytocin is released in response to the afferent nervous stimuli of dilatation of the cervix (Ferguson's reflex) and suckling. Ferguson's reflex is a positive feedback system which results in full dilatation of the cervix during labour. The suckling reflex results in contraction of the breast alveoli and milk-ejection into the ducts and sinuses. Oxytocin has the secondary effect of causing increased LTH release via its release into the hypophysial portal vessels which supply the adenohypophysis.

HYPOTHALAMIC REGULATION OF THE HORMONES OF THE ADENOHYPOPHYSIS

As mentioned before there are releasing factors which control anterior pituitary secretion. Before discussing these individually it is pertinent to describe the necessary and sufficient conditions for the existence of releasing factors. These are listed below. It is also necessary to state that none of the releasing factors to be described fulfills all these criteria as yet, and thus it is not possible to fully understand or describe their precise modes of action.

Criteria of Releasing Factors (RF's)

1. Material must be extracted from hypothalamic nuclei or from the median eminence.

2. The RF must be found in the portal blood of the hypothalamic-hypophysial portal system (HHPS).

3. The substance must produce increased hormone secretion with a linear relationship between response and log dose of the material injected.

4. The substance must be demonstrable in vitro.

5. The RF must act in an animal whose secretion is blocked by drugs or hypothalamic lesions, assuming otherwise normal organ function.

6. There must be no effect in the hypophysectomized animal.

7. Hypothalamic concentrations must vary with physiological states—to show a feedback system of control.

8. Indisputable criteria are required to measure the actions of the hormones released (physiological validation).

9. The RF must not act as a peripheral potentiator.

ACTH SECRETION

ACTH is produced by the beta-1 cells of the anterior pituitary in response to Corticotrophin Releasing Factor (CRF). CRF causes ACTH release and results in increased corticosterone secretion from the adrenal cortex. Vasopressin has also been found to have ACTH releasing effects but acts directly on the hypothalamus to cause release of CRF. The CRF release is an inverse feedback system with increased plasma levels of corticoids causing a decrease in CRF release. The control system has been described as sluggish; neural stimulation under stress causes wide fluctuations in ACTH release via CRF. CRF release is decreased by hypothalmic depressants such as morphine, and by a secretion from the pineal gland, probably melatonin (to be discussed later). It is increased by stress, salicylates, reserpine and chlorpromazine. CRF is actually composed of three types of molecules, all with ACTH releasing ability: alpha-1-CRF, alpha-2-CRF and beta-CRF. Beta-CRF has 50-100 times the ACTH releasing ability in equal concentration; it is, however, found in very low concentrations compared to the levels of alpha-CRF's and it is still not certain which of these plays the most important role physiologically. The role of the amygdala will be mentioned later. One can postulate a "stress-stat" in the hypothalamus which raises the threshold of the pituitary driving mechanism so as to allow increased ACTH release under stress in spite of the inverse feedback system which would depress ACTH secretion.

LH SECRETION

Luteinizing Hormone (LH) is produced and released by the delta-1 cells of the anterior pituitary gland. It is stored and secreted in response to a polypeptide, LRF, a specific releasing factor derived from the basal tuberal nucleus of the hypothalamus. LRF release is decreased by atropine, barbiturates, and hypothalamic lesions. Controls of LH secretion via LRF are listed below.

1. Environmental

(a) *Light* acts like a lesion in the hypothalamic supra-chiasmatic region to prevent LH secretion — the delta-1 cells cannot secrete the ovulatory burst of LH needed for ovulation.

(b) *Lactation.* Via the suckling reflex LH secretion and release are decreased during lactation.

(c) *Stress.* Via the hypothalamus discharge of LH is inhibited.

2. Estrogen

There is a positive feedback system, wherein low levels of estrogen cause increased LH release and a negative feedback system, wherein high levels cause decreased secretion. This mechanism is probably responsible for the cyclic shift in intact females. The estrogen exerts its effect via receptor sites in the basal tuberal nucleus of the hypothalamus and the anterior pituitary directly, but the former is more significant physiologically. It is possible that estrogen (via the hypothalamus) has a negative feedback effect and a positive effect by acting directly on the pituitary, or by increasing sensitivity to LRF.

3. *Progesterone* inhibits LH release only in the presence of estrogen, possibly via the hypothalamus.

4. *Testosterone* also has a negative feedback effect on LH secretion.

The onset of puberty is due to a decreased sensitivity of the inverse feedback system of the hypothalamic sites to the circulating estrogen; when this occurs there is increased LH secretion via LRF and puberty is initiated. LRF also acts to inhibit secretion of LTH, in the non-pregnant female.

FSH SECRETION

Follicle stimulating hormone (FSH) is released from the delta-2 cells of the anterior pituitary gland in response to FSH—releasing factor (FSH-RF, FRF) from the hypothalamus. This factor has not been characterized as yet, but has been shown to be present in hypothalamic extracts and *in vitro* to produce increased

FSH pituitary content. FSH levels are cyclical and are lowered by increased estrogen levels. The estrogen acts via the hypothalamus on FRF or possibly on the pituitary directly to decrease release of FSH or decrease sensitivity to FRF.

TSH SECRETION

TSH is released from the beta-2 cells of the anterior pituitary in response to its specific releasing factor produced in the hypothalamus, TRF. There is a negative feedback system operating with increased thyroxin producing decreased TRF release. The thyroxin probably acts by affecting the pituitary directly and the hypothalamus only slightly, but it is possible that it acts by decreasing the sensitivity of the pituitary to TRF; response is rapid and effective. TSH is released in response to both LSD and adrenaline via the hypothalamic stimulation of these drugs and TRF. TRF is a polypeptide which has had its amino acid sequence determined; it is stored in the neuro-hypophysis, and is secreted into spinal fluid, the systemic circulation and the hypothalamic-hypophysial portal system. Vasopressin, and alpha and beta-MSH also exert a direct effect on the thyroid gland and result in increased thyroxin secretion, but this is not significant in physiological doses.

GH (STH) SECRETION

Growth hormone is secreted by the acidophil cells of the anterior pituitary in response to STH-releasing factor (SRF). There is evidence that there are glucoreceptors in the hypothalamus and that a decrease in blood glucose causes increased SRF secretion and results in increased STH blood levels. STH is decreased by hypothalamic depressants (eg. morphine), adrenal corticoids, pineal gland hormone and is increased by hypoglycemia and thyroxin. The relationship of STH secretion to CNS control of growth is not fully understood, but it is possible that by analogy there is a "stat" in the hypothalamus which is responsible for control of STH via the secretion of SRF into the hypothalamic-hypophysial portal system, and the anterior pituitary release of STH.

PROLACTIN (LTH) SECRETION

LTH is synthesized, stored and released from the acidophil cells of the anterior pituitary gland. The hypothalamus secretes a substance (PIF), prolactin inhibiting factor which exerts a tonic *inhibition* on LTH secretion. The PIF inhibits release of LTH from the pituitary and prevents sucking or stress-induced falls in pituitary LTH. Secretion of LTH during lactation is maintained by sucking-induced removal of hypothalamic inhibition: i.e. PIF secretion is halted and LTH is released as the efferent limb of an LTH releasing reflex of which sucking is the afferent limb. LTH increases in concentration in late pregnancy and parallels lactation post-partum. LTH secretion is decreased by hypothalamic depressants (e.g. morphine) and is increased by all steroids in high doses, hypothalamic stimulants, and by decreased thyroxin levels (acting on the pituitary directly).

MSH SECRETION

MSH is produced by the basophils and possibly by a cell which is identical to the ACTH secreting cell, the beta-1 cell. The MSH is synthesized and stored predominantly in the pars intermedia. Control exerted by the hypothalamus on the pars intermedia is achieved through monoamines released into the pars intermedia, and not via neurosecretions of the neurohypophysis. Monoamines (e.g. adrenalin) exert an inhibitory effect on the secretion of MSH. The regulation requires an intact hypothalamic-hypophysial pathway.

PORTIONS OF THE CNS (OTHER THAN THE HYPOTHALAMUS) WHICH AFFECT PITUITARY ACTIVITY

1. Pineal gland

(a) secretes a hormone as yet unidentified which results in decreased STH levels in the blood.

(b) secretes a hormone, probably melatonin which results in decreased systemic levels of ACTH.

2. Pars Intermedia of the Pituitary

Secretes a substance which has corticotrophic activity and has been called Intermedin.

3. Amygdala

(a) the medial amygdaloid nucleus, when destroyed, causes increased ACTH levels in the pituitary and in the plasma, and results in increased adrenal corticosterone production which is maintained for weeks (in the deermouse). This implies the possibility of an inhibitory center to regulate the pituitary-adrenal axis.

(b) There is a similar inhibitory effect by the basolateral amygdaloid group with respect to pituitary and plasma LH.

Whether these effects are mediated by neural or hormonal causes is as yet undetermined.

SUMMARY

In summary, it can be said that the hypothalamus is the principle CNS regulator of pituitary activity. In some cases it is an activator and in others it is an inhibitor. It exerts its control over the pituitary primarily by its neurosecretions. It, in turn, is regulated by the end results of the effects of these very secretions and by its afferent nerve supply from the peripheral nervous system and from its numerous connections with other parts of the CNS. It is not, however, the sole controller of pituitary activity and recent research is indicating increased roles of the other parts of the CNS as discussed above. The complete picture of the relationship of the CNS to the pituitary, and the mechanisms of their interrelationships await the investigators of the future.

Selected references on this subject may be obtained by the interested reader upon request from the author.

Human Placental Lactogen

H. Vellend 6T8

INTRODUCTION

The marked metabolic and hormonal changes which take place during pregnancy have for a long time been attributed to the appearance of a new endocrine organ, the placenta. Although evaluation of its function in humans has been hampered by the concurrent alteration in maternal endocrine function as well as the presence of the fetus which creates a highly complex, interacting fetal-placental-maternal unit, recent studies on this remarkably versatile endocrine organ (with the possible exception of the hypothalamus, *the* most versatile) have yielded a plethora of experimental evidence regarding the nature and physiology of placental hormones. In an exhaustive review of this subject as recently as 1961, Diezfalusy and Troen[1] stated that, "there was unequivocal evidence of production by the human placenta of only three hormones, namely human chorionic gonadotropin (HCG), estrogen and progesterone." Although the lactogenic and somatotropic capabilities of placental extracts have been known for years it was not until 1961 that Ito and Higashi[2] and subsequently Josimovitch and Maclaren[3] in 1962 and Kaplan and Grumbach[4] in 1964 presented evidence that the human placenta produces a protein similar to human pituitary growth hormone (HGH), which also has lactogenic properties. It was found in relatively large amounts in the placenta as well as both the peripheral maternal and retroplacental serum. This protein has been provisionally designated as human placental lactogen[10 11] (HPL) although other authors have proposed a less-widely accepted term, chorionic growth-hormone prolactin[4] (CGP).

PROOF OF PRODUCTION BY THE PLACENTA

(1) The presence of HPL in human tissues and bodily fluids is invariably associated with the presence of chorionic tissue. It has been found in the placenta, amniotic fluid, maternal serum and urine in normal pregnancy, in molar pregnancy and in cases of embryonic testis tumors which contain cells related to chorionic epithelium.

(2) By the use of immunohistochemical techniques, this hormone has been located in the cytoplasm of the syncytiotrophoblast of the villous epithelium.

(3) Placental tissue cultured *in vitro* maintains the capability to synthesize HPL.

(4) HPL disappears rapidly from maternal serum and urine following delivery of the placenta.

(5) High concentrations of HPL are present in the serum of hypophysectomized pregnant women.

(6) Gusdon[5] has described the incorporation of C^{14}-labelled amino acids into HPL *in vitro* and subsequent identification of the product by immunochemical methods.

NATURE OF HPL

Many techniques have been described for preparing HPL with a relatively high degree of purity (homogenous on gel filtration, disc electrophoresis and analytical ultracentrifugation). Ultra-centrifugation studies have yielded a molecular weight of 37,500 to 39,000 and quantitative N-terminal data show a minimum M.W. of 21,500. The C-terminal amino acid is phenylalanine and the N-terminal is valine. Catt[13] *et al* have determined the N-terminal sequence of 17 amino acids utilizing a protein sequinator and eleven of them are identical to HGH, thus providing a structural basis for the immunologic, antigenic, and somatotropic effects of HPL.

ASSAY

Radioimmunoassay techniques have been devised for measuring microgram quantities of HPL in plasma and urine. Absolute levels are difficult to quote because there is no universal standard.

CONCENTRATION OF HPL IN BODY FLUIDS

(1) Normal Pregnancy

Maternal serum HPL is detectable at 8 weeks and the concentration rises progressively from early pregnancy to term. There seems to be no correlation between placental weight and HPL levels at term but there is a close parallel with urinary estriol excretion in the maternal urine. This has led to the suggestion that HPL levels may be an index of placental metabolism and function. This secretion pattern is in striking contrast to that of HCG which peaks sharply at day 70 and then falls off rapidly to plateau levels throughout the remainder of the gestational period. HPL disappears rapidly from the circulation following delivery and is virtually absent after 24 hours.

The concentration of HPL is 300 times greater in the maternal vein than in the umbilical vein, and the concentration in the ovarian vein is 2-5 times the concentration in the peripheral venous serum. Therefore HPL is confined largely to the maternal compartment and is not freely transported across the placental barrier.

Dynamic studies have shown a mean plasma half-life of 18.9 min., a metabolic pool size of 7.2% of the total body water, and a turnover rate of 175 ml./min.

The mean plasma concentration at term is 1.15 ug./ml., the total daily production 290 mg./day; and the daily urinary excretion at term is less than 100 ug./ml.[8] Therefore HPL seems to be rapidly catabolized.

(2) Abnormal Pregnancy

As mentioned previously, HPL is present in the serum of molar pregnancies, and in embryonic testis tumors which contain chorionic tissue. There is no difference in normal and diabetic pregnancies but in one case of fetal death *in utero* in a diabetic mother, a drop in serum HPL levels occured prior to the loss of the fetus.[12] However, many more clinical studies will have to be performed before the clinical value of HPL levels in serum and urine during normal and abnormal pregnancy can be established.

CONTROL OF SECRETION OF HPL

There is no evidence as yet available to point to distinctive mechanisms by which the production and release of HPL by the placenta is controlled.

PHYSIOLOGICAL ROLE

(1) Lactogenic or Mammotropic Effects

Turkington and Topper[7] have demonstrated on the mouse mammary gland *in vitro* that HPL synergizes with insulin and hydrocortisone to induce (a) a mature secretory alveolar structure of full-term pregnancy and (b) increased casein (a milk phosphoprotein) synthesis with 90% of the efficiency of pituitary prolactin. In addition, HPL causes increased milk producing activity in the pseudopregnant rabbit mammary gland (the basis of HPL bioassay) and is similar to pituitary prolactin in increasing DNA synthesis. Patients with choriocarcinoma of the testis exhibiting gynecomastia have an extremely high concentration of HPL in addition to increased levels of circulating estrogens.

In summary, even though there is no direct evidence that HPL produces changes in the mammary gland during gestation, it probably has an influence on breast development but the rapid disappearance of HPL after delivery precludes any sustained action during lactation.

(2) Somatotropic Effects

Although HPL cross-reacts with anti-serum to HGH, their separate identities have been established by physiochemical, immunochemical and bioassay studies. Nevertheless, this does suggest that the HGH-like metabolic changes in pregnancy might be attributable to the action of HPL, including increased maternal storage of nitrogen and minerals, and increased mobilization of fat to meet requirements for fetal growth and development. This somatotropic effect is free of the neural regulatory mechanisms of the maternal adenohypophysis and the momentary demands of the fetus.[11]

During normal pregnancy, resistance develops to the hypoglycemic action of insulin characterized by (a) impaired reduction in glucose concentration due to exogenous insulin infusions and (b) increased insulin response to glucose and tolbutamide. The magnitude of this resistance increases progressively during pregnancy and disappears rapidly in the puerperium. Since this corresponds to the secretion pattern of HPL, the metabolic effects of this hormone have been studied and the following observations have been made: (a) HPL antagonizes the hypoglycemic action of insulin similar to that seen in acromegalics and exogenous HGH infusion; (b) HPL reduces glucose tolerance in cortisone treated hypophysectomized rats; (c) HPL causes increased free-fatty acid (FFA) release in hypopituitary patients; (d) HPL promotes lipolysis in isolated fat cell preparations; (e) HPL impairs glucose metabolism in hypophysectomized diabetic patients; (f) Beck and Daughaday[8] have demonstrated in normal non-pregnant subjects, after prolonged ($>$ 12 hrs.) infusion of HPL in physiological concentrations, impaired peripheral glucose utilization and increased release of FFA.

Part of the effect of HPL on glucose and insulin metabolism may be due to steroid hormones secreted by the placenta. This observation is supported by evidence that normal women on norethynodrel plus mestranol show impaired insulin response to glucose and have a higher incidence of abnormal glucose tolerance curves. Also, HPL action may be mediated by a potentiation of HGH in rats in preventing insulin induced hypoglycemia.[9]

Therefore it seems certain than HPL is a significant physiological antagonist of insulin and consequently its effect has been invoked as a possible explanation of the diabetogenic features of normal pregnancy.

SUMMARY

Throughout gestation, the human placenta elaborates a biologically active polypeptide called HPL, which has both lactogenic and growth hormone-like effects. The evidence for its placental production is now conclusive. Its chemical nature, including partial amino acid sequence determination has been incompletely elucidated. Maternal serum HPL levels rise progressively from early pregnancy to term and disappear rapidly following delivery. The hormone is largely confined to the maternal compartment. Control mechanisms for its secretion are not known. HPL probably has mammotropic effects during pregnancy and its HGH-like properties have been invoked to explain maternal nitrogen retention, fat utilization, as well as certain of the diabetogenic features of normal pregnancy. The clinical usefulness of HPL assays remains to be established.

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Endocrine Disorders Produced By Non-endocrine Malignant Tumors

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It has become increasingly evident that certain malignant tumors may produce endocrinopathies without having their origin in endocrine glands and without secondarily invading them. These so-called "non-endocrine" tumors have been found to secrete substances that, like ordinary hormones, are carried by the blood stream to other tissues where they exert biological effects and produce recognizable clinical syndromes. Although definite proof by direct hormone assay of the tumor is lacking in some instances, there is adequate evidence that these tumors can produce substances that mimic the actions of adrenocorticotropin (ACTH), melanocyte-stimulating hormone (MSH), parathormone, thyrotropin (TSH), gonadotropin, antidiuretic hormone (ADH), insulin, glucagon, serotonin, gastrin, and erythropoietin.

ADRENOCORTICOTROPIN (ACTH)

In 1928, a case was reported of a 45-year old woman who developed the clinical picture of Cushing's syndrome and at post mortem was found to have an oat-cell carcinoma of the bronchus and bilateral adrenal hyperplasia. The carcinoma was regarded as an incidental finding but since that time it has been increasingly recognized that Cushing's syndrome may be associated with malignant neoplasms of various organs which normally do not participate in the regulation of the pituitary or adrenal glands. The neoplasms most frequently associated with this syndrome are anaplastic or oat-cell bronchogenic carcinoma, islet-cell pancreatic carcinoma, and thymoma. Numerous other reports have implicated the following neoplasms as well — mediastinal carcinoma (11 cases); malignant bronchial carcinoid tumors (5 cases); neuroblastoma (4 cases); thyroid carcinoma (3 cases); parotid carcinoma (2 cases); ovarian tumors (2 cases); carcinoma of the breast; carcinoma of the prostate; carcinoma of the testis (seminoma); parathyroid carcinoma; cancers of the esophagus, colon, and gall bladder; central nervous system tumors; and even a carcinoma of the liver and a childhood ganglioneuroma. Well over one hundred cases of extra-adrenal and extra-pituitary malignancy with Cushing's syndrome, commonly referred to as "combined disease" or the "ectopic ACTH syndrome", have been described to date. The relationship between the tumor and Cushing's syndrome is indisputable. In some cases in which surgical removal of the tumor was possible, regression of the symptoms occurred and then re-appeared with recurrence of the tumor or growth of metastases. This "ectopic ACTH syndrome" will be discussed at greater length than the other "combined diseases", because it is the commonest and best-documented.

The clinical presentation of these patients is extremely variable. Commonly the disease is characterized by progressive weakness, muscle wasting, and severe hypokalemic alkalosis, and is associated with a pattern of electrolyte loss suggestive of excessive mineralocorticoid activity which is extremely rare in non-malignant Cushing's syndrome. Some present with oedema. The clinical picture does not usually suggest adrenal hyperactivity, but the biochemical findings in the urine and plasma and the post mortem findings are typical of severe adrenocortical overactivity. Mental changes and increased skin and mucous membrane pigmentation are more likely with combined disease; however, obesity, striae, and osteoporosis are less common. Carbohydrate intolerance and ecchymosis occur equally in non-combined and combined disease. In a few patients, who develop all the classical clinical features of Cushing's syndrome, the primary neoplasm is likely to be mediastinal, thymic, pancreatic, or a relatively slow growing carcinoid. Many of the usual features are not present in combined disease, especially in rapidly growing bronchogenic carcinomas. This is due to either insufficient time for development prior to death, or masking by the weight loss accompanying the cancer. Those who survive long enough and eat enough, do develop florid Cushing's syndrome. Clinical evidence of adrenal cortical overactivity may appear before the underlying malignancy, but more commonly it follows the removal or irradiation of the primary tumor and is due to a recurrence or the growth of hormone-secreting metastases. The combined disease differs from Cushing's syndrome in certain other ways also. Rapid progression of the clinical course is characteristic, the average duration from first symptom to death being nine months as opposed to about five years with untreated Cushing's syndrome. Approximately 15% of cases do have a more prolonged course. The sex ratio is about equal (except of course, with bronchogenic carcinoma), whereas Cushing's syndrome occurs more commonly in females. The average age of onset of combined disease is 52 years; that of non-malignant Cushing's is 32 years.

A laboratory finding included in all classic descriptions of Cushings' syndrome—a low serum potassium level and elevated carbon dioxide content—is rarely found in practice. However, this hypokalemic alkalosis is a predominant feature of combined disease and may be out of proportion to the other features of the disease. In fact, if one finds hypokalemic alkalosis as a present-

ing sign in a patient with Cushing's syndrome, one should search for a malignant tumor. This electrolyte disturbance has led to speculation that aldosterone production is disproportionately increased but there is no satisfactory evidence for this.

The adrenals in all cases of combined disease are hyperfunctioning and show bilateral benign hyperplasia. They attain an average size greater than that seen in most cases of Cushing's syndrome and average more than 30 gms. (normal weight about 8 gms.). In non-malignant (bilateral) hyperplasia (75% of cases), the glands are usually less than 20 gms. in weight.

Pituitary-adrenal function studies have helped to clarify the patho-physiology of combined disease. Normally, the cortisol feedback mechanism, via the hypothalamus and corticotropin releasing factor, controls ACTH release by the anterior pituitary, and in turn the plasma level of cortisol. In non-malignant bilateral adrenal hyperplasia an abnormality of this mechanism permits ACTH production to continue despite elevated levels of plasma cortisol. With adrenal adenomas and carcinomas the feed-back mechanism is efficient and virtually no ACTH is released; however, the plasma cortisol, which produces the clinical features of Cushing's syndrome, is maintained at a higher level due to excess production by the adrenal tumor. The increased ACTH production is combined disease is due to production of an ACTH-like hormone by the malignant tumor that is released directly into the blood stream. Material extracted from these tumors is biologically, physically, and immunologically indistinguishable from human pituitary ACTH. Because of the very limited quantity of the ectopic ACTH available for study, it has not been possible to analyze its amino acid composition. This substance need not be identical to human pituitary ACTH (a single chain polypeptide of 39 amino acids) because it has been proven that the first 24, 19, 17, and even 13 amino acids of the sequence have steroidogenic activity. In the cases in which the plasma ACTH level was determined it was found to be elevated, yet when studied, the pituitary glands have been found to contain *decreased* amounts of ACTH. It should be noted that no secondary tumor deposits were discovered either in the region of the pituitary or the hypothalamus. The ACTH-like substance produced by these tumors results in elevated plasma ACTH levels inducing hyperplastic adrenal cortex changes, excessive cortisol secretion, and in turn, suppression of pituitary ACTH secretion and the clinical features of Cushing's syndrome. The tumor secretes its hormone despite excessive levels of endogenous cortisol or despite administration of dexamethasone. With a dose of 2 mg. of dexamethasone every six hours for two days, ACTH production and the amount of urinary 17-keto and 17-OH steroids is decreased with non-malignant bilateral adrenal hyperplasia, but this does not occur with either combined disease, an anterior pituitary tumor, or an autonomous adrenal tumor. The metapirone (metyrapone) test may also be useful in differentiating between combined disease and adrenal hyperplasia. In this test patients with Cushing's syndrome due to benign hyperplasia or an adrenal adenoma exhibit a greater response than normal, but patients with combined disease or an anterior pituitary tumor show a variable response depending on whether or not the adrenals are maximally stimulated all the time. With adrenal carcinomas, there will be a minimal or no response if the tumor is autonomous, or an increased response as with adenomas if it is not. The results of the ACTH stimulation test are similar to those of the metyrapone test since both are related to an increased ACTH plasma level. In all cases of combined disease baseline urinary excretions of 17-OH steroids are elevated, frequently to levels greater than those attained in benign adrenal hyperplasia. Despite these tests, an unequivocal diagnosis of the ectopic ACTH syndrome cannot be established unless a significant quantity of ectopic tumor ACTH is demonstrated. In its absence only a presumptive diagnosis can be made.

Nine per cent of patients with bronchial carcinoma have been found at autopsy to have adrenal weights above normal and cortical hypertrophy, without associated Cushing's syndrome. For this reason it is now postulated that there are two types of ectopic ACTH—a steroid releasing type that causes Cushing's syndrome, and a weight-maintaining type that causes adrenal cortical hypertrophy. This would account for the cortical hypertrophy but lack of Cushing's syndrome in these patients.

The treatment of choice for the ectopic ACTH syndrome is removal of the malignant tumor, but if it is inoperable, palliative bilateral adrenalectomy may be considered with slowly growing tumors. Irradiation of the primary tumor is usually of little value because of the development of metastases. Subtotal bilateral adrenalectomy is disappointing; however, long-term administration of metyrapone has helped in some inoperable cases with rapidly growing tumors.

MELANOCYTE-STIMULATING HORMONE (MSH)

The alpha and beta melanocyte-stimulating hormones are close chemical relatives of ACTH which itself has some melanocyte-stimulating activity. To date, at least nine cases of Cushing's syndrome resulting from combined disease were associated with increased pigmentation. However, a pancreatic tumor from a patient with combined disease was found to contain MSH activity 1600 times that expected from its ACTH content. It was suggested that the tumor produced polypeptides resembling MSH, in addition to ACTH (resembling pituitary ACTH).

PARATHORMONE

Hypercalcemia, hypophosphatemia, and elevated alkaline phosphatase levels accompany a wide variety of

carcinomas and mimic hyperparathyroidism. If skeletal metastases were overt, these findings could be expected. However, at least 79 cases of hypercalcemia associated with cancer have been reported in which no bone involvement could be demonstrated. Fourteen of these were breast cancer, 12 were malignant lymphomata, 10 were hypernephromas, 9 were bronchogenic in origin (usually squamous-cell), and the rest occurred in isolated miscellaneous tumors. There was no gross or microscopic evidence of parathyroid enlargement or hyperactivity in any of these cases. In many instances, removal of the tumor was associated with return of the serum calcium values to normal, and recurrence with reappearance of hypercalcemia.

In 1964 a parathormone-like substance was first identified in a primary renal adenocarcinoma and a distant lung metastasis. This substance specifically inhibited direct complement fixation by purified bovine parathyroid hormone and anti-bovine parathyroid hormone. Immunoassay has shown this substance to be indistinguishable from parathormone. An increased circulating level of parathormone has been demonstrated only in some cases of hypercalcemia associated with malignancy. Other tumors (without bone metastases) have not been found to contain measurable increased amounts of parathormone, and other mechanisms must be responsible for the hypercalcemia in these patients.

The resulting hypercalcemia produces weakness, lethargy, obtundation, mental changes, depressed intestinal motility, hypoactive tendon reflexes, a high C.S.F. calcium, and a shortened QT interval on ECG. These cases are difficult to differentiate from primary hyperparathyroidism but the rapidly progressive course with combined disease may be of diagnostic value. Tubular reabsorption of phosphate, calcium infusion, and steroid suppression tests are of little value.

THYROTROPIN (TSH)

Hyperthyroidism too has been noted in association with malignant tumors. There is a well-documented association of hyperthyroidism with trophoblastic tumors and three reports of hyperthyroidism with hydatidiform mole have been confirmed by appropriate thyroid-function tests. In each case delivery of the mole was followed by subsiding of the hyperthyroidism. Similar findings have been reported in seven women with metastatic choriocarcinoma and in one male with embryonal carcinoma of the testis. In four of the patients with metastatic trophoblastic disease, plasma TSH activity was increased when measured by a bioassay technique, and in two of these patients the plasma TSH levels were elevated and extracts of the tumor tissue contained large amounts of a TSH-like material. These tumors were autonomous since exogenous thyroid did not suppress the I^{131} uptake. On the basis of these cases, it seems likely that tumors of germ-cell origin in both males and females can elaborate a substance with TSH activity in addition to the hormones they characteristically produce. Since the hyperthyroidism produced is usually clinically mild, the syndrome may be considerably more common than is recognized.

GONADOTROPIN

Precocious puberty has been observed in eight male children ranging in age from 1 to 8 years, in association with hepatoblastoma. In all cases, there was evidence of penile development and early maturation of secondary sex characteristics. When measured, gonadotropins were found to be increased markedly in the blood or urine. Interstitial cells were present in the testes and an increased excretion of testosterone was demonstrated in one case.

It is clear that the precocious puberty was due to the production of a substance with interstitial cell stimulating properties, probably by the tumor. Since tubular development did not occur, presumably there was no FSH-like substance present. Treatment of the hepatoblastoma by surgery, irradiation, and methotrexate resulted in a remission of the precocious puberty in several cases.

These tumors were histologically the same as the other childhood hepatoblastomas in which virilization does not occur. In no instance were teratoid structures or trophoblastic cells encountered that could be implicated as the source of the gonadotropin.

ANTIDIURETIC HORMONE (ADH)

The hyponatremia associated with oat-cell carcinoma of the bronchus has been attributed to excessive production of ADH by the tumor leading to dilutional hyponatremia. Evidence for this is that the urine osmolality is persistently greater than that of the plasma in the presence of normal hydration or over-hydration and low plasma osmotic pressure. The only substance known to be capable of stimulating renal water absorption against an osmotic gradient is ADH. Since the normal response to low plasma osmolality is depression of ADH secretion, presence of the hormone in these cases is "inappropriate".

At least 19 cases of carcinoma of the lung with inappropriate antidiuresis have been reported and at least nine of them were oat-cell in type. The pathogenesis of this syndrome is obscure but a vagal neurogenic basis (the tumor causing vagal stimulation and in turn stimulation of the hypothalamus and ADH release from the posterior pituitary) has been postulated. Antidiuretic activity in the blood and even higher concentrations of an ADH-like substance in the tumors, has been demonstrated in several of these cases. Although the material has some of the properties of arginine vasopressin (ADH), it is premature to conclude that it is identical with it.

INSULIN AND GLUCAGON

At least 100 patients have been reported with hypoglycemia secondary to *non*-pancreatic tumors. The tumors are usually large and fibrous, of mesodermal origin, and more than 80 per cent have occurred in the abdomen. The retroperitoneal fibrosarcoma is the most common; however, a wide variety of neoplasms have been associated with hypoglycemia, most notably hepatic and adrenal cortical carcinomas. The etiology is unknown but is believed due to either the elaboration of an amino acid with a hypoglycemic action differing from that of insulin, or by secretion of insulin or an insulin-like substance by the tumor, or the removal of abnormally large amounts of glucose from the blood by large tumors for their metabolism. Insulin-like activity has been demonstrated in some, but not all tumors in which its presence was sought. In only one case has this substance been identified as insulin. Extracts of a liver metastasis from an undifferentiated bronchogenic carcinoma were found to contain remarkably high concentrations of insulin by highly specific radio-immunochemical techniques. The substance could not be differentiated from the pancreatic hormone. From the same tumor metastasis, large concentrations of glucagon were also found. Again, specific immunochemical and physiochemical techniques failed to prove that the tumor glucagon differed from pancreatic glucagon.

The prolonged hypoglycemic response produced by tolbutamide in patients with pancreatic islet-cell adenomas is a reasonable diagnostic tool in differentiating it from a non-pancreatic neoplasm. Careful palpation of the abdomen is also important since, as mentioned earlier, the sarcomas are usually very large and grow slowly, sometimes permitting surgical resection.

SEROTONIN

The carcinoid syndrome due to malignant carcinoid tumors of the small intestine with metastases to the liver is now clearly defined. The syndrome of flushing, asthma, diarrhea, abdominal cramps, lacrimation, fundal lesions and borborygmi has been shown to be due to the production of serotonin (5-hydroxytryptamine) by the tumors. The metabolism of serotonin to 5-hydroxyindoleacetic acid (5-HIAA) which is excreted in the urine, provides an excellent diagnostic test.

The primary carcinoid tumors have been found in extra-intestinal sites including the bile ducts, pancreas, ovaries, and bronchi. Some of these tumors secrete large amounts of histamine and 5-hydroxytryptophan as well as serotonin, and the clinical syndrome may not be typical. The atypical and typical carcinoid syndromes have also been reported with pancreatic duct-cell carcinoma, bronchogenic oat-cell carcinoma, gastric carcinoma, and neuroblastoma. The bronchial carcinoids are not infrequently associated with Cushing's syndrome, acromegaly, and pluriglandular adenomatosis. All these are additional examples of hormone producing non-endocrine tumors.

GASTRIN

Gastrin is a hormone which is normally produced in the antral mucosa of the stomach and possibly in the intestinal mucosa. It stimulates the secretion of acid and pepsin, and increases gastric tone and motility.

In 1955, Zollinger and Ellison described a symptom triad of persistent peptic ulcer, gastric hyperacidity, and noninsulin-producing islet cell pancreatic tumors. A gastrin-like substance from extracts of such tumors is capable of producing gastric acid secretion in experimental animals. Removal of the pancreatic tumor resulted in healing of the previously intractable ulcer in all known human cases. Recently there have been at least three cases of the Zollinger-Ellison syndrome in which a circulating secretagogue could be demonstrated.

ERYTHROPOIETIN AND THROMBOPOIETIN

Polycythemia without associated increase in spleen size, white cell count, or platelet count has been noted with certain neoplasms that include cerebellar hemangioblastomas, uterine fibroids, pheochromocytomas, and hepatomas. Since the kidney is normally the important source of erythropoietin, erythremia assóciated with renal carcinomas and benign renal lesions is analogous to hypoglycemia associated with a pancreatic islet-cell tumor. Resection of any of the above mentioned tumors resulted in a return of the elevated red cell count, haemoglobin, and hematocrit to normal in many cases.

Normally, erythropoiesis is stimulated by the mucoprotein hormone, erythropoietin, in response to anoxia and anemia. Erythropoietin, physiochemically and immunochemically identical to the "normal" hormone, has been demonstrated in extracts of cerebellar hemangioblastoma and pheochromocytoma (as well as renal tumors). This hormone has also been found to be increased in the sera of some of these patients. It is most likely that the polycythemia associated with these tumors is secondary to tumor production of erythropoietin or an erythropoietin-like substance. Thrombopoietin production resulting in cases of isolated thrombocytosis, have also been reported with the same non-endocrine tumors.

CONCLUSIONS AND THEORETICAL ASPECTS

The endocrine dysfunction of these non-endocrine tumors appears to be related partly to the histology of the tumor since hypoglycemia is seen mostly with mesenchymal neoplasms and the other "hormones" are seen mostly with carcinomas. Carcinoma of the bronchus accounts for the largest proportion of cases. Occasionally the tumors elaborate more than one substance and result in more than one syndrome.

ENDOCRINE DISORDERS PRODUCED BY NON-ENDOCRINE MALIGNANT TUMORS

Although specific hormones have been identified in tumors, direct evidence of production of these hormones by the tumors is lacking. It has been suggested these tumors may act as a sponge (certain malignant tumors have been shown to have an increased avidity for certain proteins), accumulate hormone, and then release large quantities of it with accelerated breakdown of the cancer or other tumor. Thus the presence of the hormone in the tumor cells does not necessarily mean the tumor produced it.

Although the riddle of the "humor in the tumor" is far from being solved, a few additional hypothetical mechanisms have been suggested:

1. The most sophisticated is based on the fact that *all* cells in an organism are endowed with DNA coding the *same* information, and hence potentially have the same capacity to synthesize functional and structural polypeptides. Normally, cell differentiation involves *repressing* a large number of DNA units (genes) and *expressing* others.

It is postulated that neoplastic transformation permits synthesis of proteins and polypeptides by a *de-repression* phenomenon, which removes the controls normally preventing each cell from utilizing all the information coded on its complement of DNA.

2. At the other end of the spectrum, *random* synthesis of biologically active polypeptides is also possible. This is akin to the old saying that, "if an infinite number of monkeys banged away randomly on an infinite number of typewriters, they would come up with all the works of Shakespeare!"

Many questions remain unanswered about these syndromes associated with malignant disease, but time and continued research will hopefully be able to answer them.

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WEBSTER PRIZE FOR 1967-68

The editors are pleased to announce that M. E. Rogers has been awarded the Webster Prize for the best article in the University of Toronto Medical Journal for the year 1967-68. Her article, entitled Psyche and Soma: The Interrelation of Psychiatric and Endocrine Diseases, which appears on page 178 of this issue, was selected on the basis of originality, journalistic quality, and interest to the reader. Congratulations are extended to Mrs. Rogers on this account.

The prize of fifty dollars was endowed by Mrs. Annie Webster in memory of Dr. J. D. Webster, and is awarded annually at the Academy of Medicine Library and Historical night. We wish to thank the Academy of Medicine for their interest in the undergraduate body and in particular, for their promotion of student journalism.

* WEBSTER PRIZE WINNING ARTICLE 1967-68

Psyche and Soma: The Interrelation Of Psychiatric And Endocrine Diseases

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"A sound mind in a sound body is a thing to be prayed for" — Juvenal.

INTRODUCTION

This is an era of medical optimism and scientific precision: it is an age of the study of biological minutiae. Combining these two facets in the study of psychiatric disorders, one is encouraged to consider the possibility of a biological etiology, and thereby, envision psychiatric disease as potentially curable. Witness, for instance, the vistas which would unfold if a chemical basis were discovered for schizophrenia, a chronic disease affecting 1% of our population. It is the aim of this article first, to propose an anatomical and physiological model for neuro-endocrine relationships and secondly, on this basis, to provide a classification of related psychiatric and endocrine disorders.

ANATOMY & PHYSIOLOGY

The pituitary is the chief regulator of the endocrine glands via release of the *trophic hormones*. It has neural and vascular connections to the hypothalamus.

The hypothalamus is the most significant link between the central nervous system and the endocrine system. It controls the anterior lobe of the pituitary by the secretion of the *releasing* factors, one for each trophic hormone. The hypothalamus is in the cross-fire between the limbic system and the reticular system. The limbic system is the old cortex, the vegetative cortex, the seat of emotion and affect, and the centre controlling activities basic to the preservation of life: fighting, fleeing, feeding and reproduction. The reticular system is a complex neural network in the brain core extending from the medulla to, and interconnecting with, the hypothalamus. Stimuli from the environment, transmitted via the cortex impinge on both these systems and they in turn are able to modify the function of the hypothalamus via their neural connections with it.

Functionally, hormones are released by the endocrine system in three manners.

First, hormones may be released *cyclically:* for example, by the properly functioning ovary. Secondly, there can be *reflex* release of hormones. For example, in response to the afferent neural stimulus of the suckling infant, the posterior pituitary releases stored oxytocin which causes milk let-down. Another obstetrical example is Ferguson's reflex, whereby application of the fetal head to the dilating cervix in labour reflexly causes oxytocin release, with subsequent increased tone of uterine contractions. Another example is the release of hydrocortisone from the adrenal gland in response to general biological stress (infection, illness). Thirdly, release of hormones can be regulated by a *feedback* mechanism: for example, vasopressin (A.D.H.) is released in response to an increase in plasma osmolality, which is adjudged by specific osmoreceptors in the hypothalamus. Decreased levels of thyroid hormone are an impetus for the pituitary to release thyrotrophic hormone, which in turn stimulates the thyroid gland to manufacture and release more thyroid hormone.

CLASSIFICATION

On the basis of anatomy and physiology one can propose two broad classes of neuro-endocrine disease.

I Psychosomatic disorders

These include any derrangement of bodily function with a drive from the central nervous system, and may be of two types. In the first type the central nervous system, specifically, the R.A.S., acts as a *generator* of internal stresses to the endocrine system: this would lead to a disturbance of the *cyclical* hormonal physiology, because of the cyclical aspect of R.A.S. function. In the second type, the central nervous system acts as a *transmitter* of external (environmental) stimuli to the endocrine system. This would lead to a disturbance of *reflex* hormone release.

II Somatopsychic Disorders

In these conditions changes in body function (specifically herein, the endocrine system) lead to psychiatric disturbances. This would entail mainly a disturbance of endocrine function regulated by *feedback* mechanisms.

I PSYCHOSOMATIC DISORDERS

1) Endocrine Diseases Induced by Internally Generated C.N.S. Stresses

The principal neuro-endocrine link proposed is the Reticular Activating System (R.A.S.). Certainly today, research into the physiology of the R.A.S. is as compellingly fascinating as that of prenatal physiology and subcellular biochemistry! For the R.A.S. would seem to be the key link between man's vegetative and cognitive functions. The major portion of this paper will discuss the implications of this statement.

Situated in the core of the brain stem and extending from medulla to hypothalamus, the R.A.S. is an intricate network of fibre tracts and multi-synaptic cells.

It receives incoming fibres from all peripheral sensory pathways, from the cerebellum, from the basal ganglia, from the limbic system, and from the cortex. As with any other part of the body, the R.A.S. can be influenced also by its biochemical milieu; so that alterations in blood constituents, glucose, electrolytes and hormones will influence its function.

In the domain of engineering, the R.A.S. would be termed a *servo* system: that is, its output is not an end unto itself; rather its output alters the function of other working systems. Specifically, descending tracks from the R.A.S. act upon spinal levels influencing postural and other activity; ascending tracts influence hypothalamic mechanisms concerned with visceral and endocrine functions; tracts extend to the diencephalon and limbic system which are deemed the seat of affect and emotion; its non-specific mechanisms extend to the neocortex, which serves higher sensorimotor and intellectual performance. All these actions of the R.A.S. are completely integrated; although here we will consider only its actions on the hypothalamus.

Manifestations of R.A.S. Activity

Ascending reticulo-cortical influences, particularly those from the cephalic end of the thalamus lead to a generalized and prolonged increase of subcortical activity; descending cortico-reticular influences can either increase or decrease the excitability of the R.A.S. Fluctuations in R.A.S. activity are postulated to be the basis of variations in sleeping and waking.

As an extension of this postulate, one might consider this variable R.A.S. activity a drive force by itself; perhaps it is the originator of the biological rhythms, specifically, for consideration here, rhythms of endocrine physiology or cyclic pathology.

The R.A.S. as a Biological Clock

Biological rhythms are well-known in modern physiology. They include such diurnal variations as sleeping and waking, body temperature and pulse rate, changes in eosinophil count, blood glucose and blood cortisol, and fluctuations in urinary excretion of sodium, potassium, and hydroxycorticoids. A longer rhythm is that of female reproductive function. As yet, however, there is no known anatomical site for the clock which times these physiological variations: but a logical choice would seem to be the R.A.S., with its all-pervasive rhythmic influences on higher neurological function, including that of the cortex, and its intimate relation to the hypothalamus, the clearing house for messages to endocrine organs.

The imposition of biological rhythm is by a process of *entrainment:* i.e., the synchronization of endogenous rhythms with exogenous regulators such as activity patterns, seasonal changes and variations in light and temperature. How the R.A.S. eventually becomes *independent* of these influences is unknown; probably it is via intricate cellular biochemical controls.

A curious fact about this "clock" is its absence in the newborn infant; but, over the first two weeks of life a diurnal pattern of sleep and wakefulness develops, after an initial period of unevenly distributed nighttime waking hours. In the fourth to ninth weeks of life a circadian (Latin—*circa dies*) rhythm of pulse and body temperature appears; by the fourth week there is a night-day differential of urine volume, and by eight weeks a variable sodium and potassium excretion.

Interestingly, the cycle of the clock is not identical in all persons; it does not follow exactly the 24-hour day, but may have a 20-28 hour rhythm. (This is why some of us don't fit into the 24 hour activities too well, as exhibited, perhaps, by always falling asleep at one particular lecture hour!) It also varies within the same individual, shifting gradually to a new schedule with changes in work, living habits or environment (e.g. climate). Gross disruptions of time zone and environment such as that afforded by rapid, long jet flights, results in desynchronization of biological rhythms, manifested in lowered mental efficiency and physical fatigue.

At puberty in the female, the cycling of reproductive function is instituted. The mechanism of its inception is not definitely known; but in lower animals, particularly amphibians, the pineal gland and its correlation with a lengthening number of daylight hours have been implicated in the achievement of sexual maturity. The entrained reticular system is probably responsible for the cyclic control of the secretion of releasing factors from the hypothalamus which act on the trophic hormones of the pituitary.

In addition to the *hormonal* aspects of the reproductive cycle, in certain animals such as the cat and the rabbit, there exists a cyclic *behavioural* aspect to the estrus. On the basis of selective obliterative or stimulatory studies, it appears that the centres for behavioural manifestations and the endocrine manifestations, though integrated, are *separate*. Therefore, dysfunction of one or other system could exist separately. In animals, there is increased activity of the R.A.S. in the initial stages of mating behaviour. Implanting hormones in this same area also produces alteration in R.A.S. activity. Taken together, these facts suggest that the induction of sexual *behaviour,* and its remarkable periodicity in these animals may be explained in terms of direct *endocrine* modification of the excitability of the brain.

It is difficult to apply these premises to human sexual behaviour, even though psychologists report a variability in female libido, with an increase immediately pre- and post- menstrually. The subtle influences of the intricate human psyche on sexual behaviour probably overshadow any primordial estrus cycle in women. More signi-

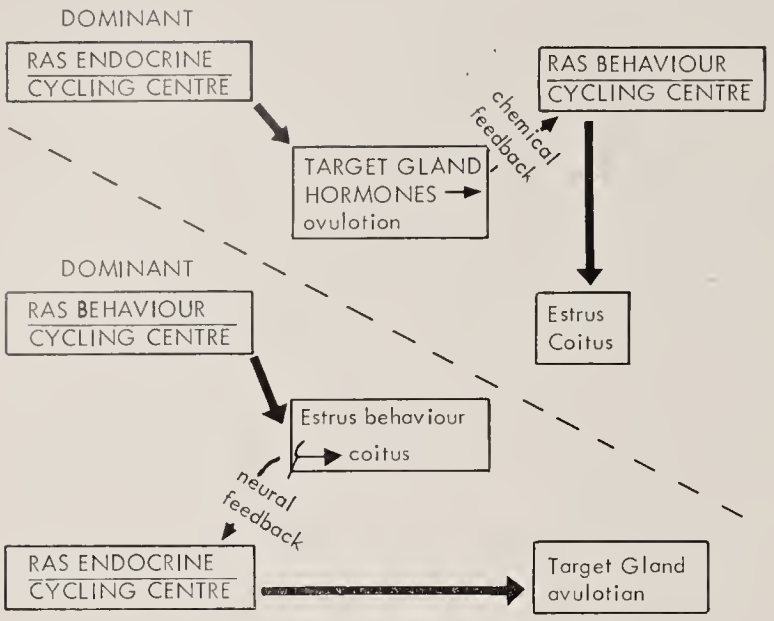

FIG. 1.

Interrelation of Behavioural and Endocrine Centres: above —"cyclic" ovulation in rat; below—"reflex" ovulation in rabbit.

ficant influences here are either the relative decrease in fertility at these times and therefore the decreased fear of pregnancy, or the prospect of, and release from the abstinence usually imposed by menstruation.

In the rat, there is also evidence for definite cycling of *alimentary* activity, and certain hypothalamic nuclei are important in the control of feeding. There may also be a negative feedback mechanism operant in this system, whereby the activity of the hypothalamic centers is inversely proportional to the level of blood glucose, serum lipids and amino acids.

So far we have postulated a R.A.S. cycling mechanism for endocrine function and certain other activities. What are some of the known human psychiatric diseases which might be possibly explained by a derrangement of this cycling centre? One example is that of the *cyclic affective disorders.*

Here we are concerned mainly with depression and, in rarer cases, with manic-depressive illness. Traditionally, the etiology of these illnesses has been related primarily to psychological determinants, but recent studies implicate endocrine disturbances as well. It must be emphasized that the results are *correlational* only, and what follows is an *attempted* explanation for their occurrence.

Depression may be the most common ailment affecting mankind. Certain patients have definitely cyclical episodes of acute depression, every two weeks, every month, six weeks, or six months without fail. During these episodes, they have a high output of urinary hydroxycorticoids, decreased urine volume, with low output of sodium and a high serum sodium. During the remission phase they have normal steroid and salt metabolism.

A case is reported of a manic-depressive patient who was investigated over a five year period. "The patient, a woman in her fifties, had a regular 21-day cycle of manic overactivity alternating with depressive stupor. The manic phase was characterized by excessive urination, deficiency of eosinophil cells, low blood pressure, and a high level of estrogen. In contrast, the depressive phase was characterized by diminished urination, an excess of eosinophil cells, high blood pressure and a low estrogen level. In both the manic and the depressed phases there was an excess of cholesterol in the blood, but it was much higher in the depressed phase."

The mechanism suggested by the generalized endocrine dysfunction, here involving adrenal, ovary and thyroid glands, is that the R.A.S. cycling center influencing hypothalamic and pituitary activity has been disturbed. It has been disturbed both for the length of cycle (e.g. for adrenal, 21 days vs. 1 day) and for degree of variation. This leads, sequentially, to abnormal target gland function, producing altered salt, water and lipid metabolism. These alterations in blood constituents cause dysfunction on a cellular level in the higher cerebral and limbic centers, as manifested by altered intellectual performance and/or emotion.

An alternative explanation is that the same maladjusted focus in the R.A.S. which produces the endocrine changes, directly influences the limbic system via *neural* connections, rather than via chemical feedback, registering again as altered performance and emotion.

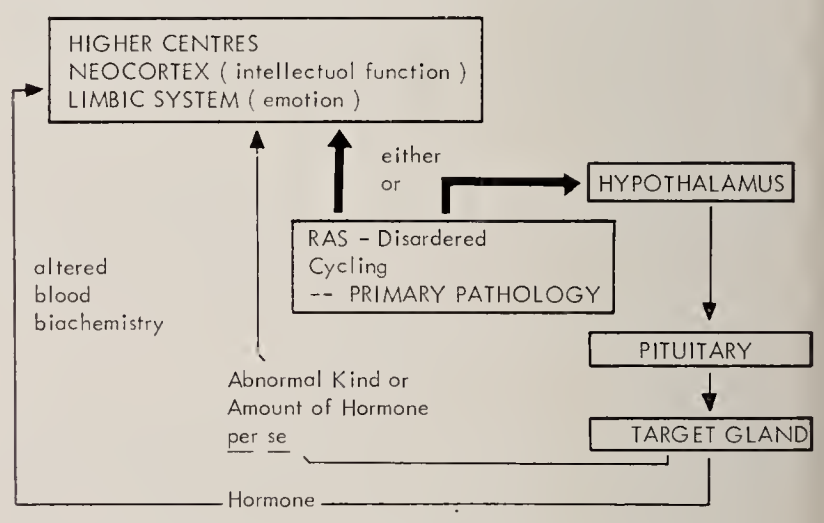

FIG. 2.

Schematic Mechanism for Etiology of Cyclic Affective Endocrine-Mediated Disorders due to Internally (RAS) Generated Stress.

It is interesting to speculate here, as to whether the cyclic nature of some schizophrenic disorders (which are lately being considered to have a biochemical etiology) have a similar R.A.S. basis.

A less esoteric disease, premenstrual tension (PMT) may bring the whole concept into better focus. This syndrome, to a greater or lesser degree, is quite prevalent in the female population of reproductive years. While its magnitude is not so gross as that of the cyclic affective disorders, the relative disruption it produces to interpersonal relationships within the context of family life, renders it greater significance.

PMT is a symptom complex of exceeding distress to the patient, occurring from three to 14 days prior to the onset of menstruation. It consists, in severe form, of such psychiatric features as inability to concentrate, impaired mental acuity, anxiety, depression, emotional instability and irritability, as well as various somatic features (headache, visual disturbances, G.I. upset, weight gain and often overt peripheral oedema). The pathophysiological mechanism is most likely excessive sodium and water retention, in turn due to improper estrogen-progesterone balance, with excessive estrogen.

As opposed to this feedback mechanism, one might consider it as an internally generated disease, with cyclical R.A.S. drive, much as the cyclic affective disorders above. Certainly the reproductive cycle which subtends PMT has a rhythm control from the R.A.S.

At present we treat the end results of these two syndromes: diuretics and tranquilizers for PMT; tranquilizers and/or mood elevators for manic-depressive psychoses. However, the ideal treatment would be to reset the biological regulators in the R.A.S., should derangement of these indeed turn out to be the case.

2) Endocrine Diseases Induced by External, C.N.S. —Transmitted Stresses

Since connections exist between the cortex and the R.A.S., and between the cortex and the hypothalamus, certain diseases could therefore be initiated by stressful stimuli from the environment or from the individual himself (his agitated personality, his wrong learning, his faulty conditioning). Via the cortex or the limbic system these stresses bombard the hypothalamus directly, causing the pituitary regulator to be disrupted. Consequently, abnormal levels of trophic hormones would cause target gland malfunction, even to the point of autonomous function.

We can tie in with this Selye's proposed "General Adaptation Syndrome". There are three parts to this theory: in reaction to constant stress there is first a stage of *reaction* (increased gland action), a stage of *resistance* (sufficient gland action for homeostasis), and finally a stage of *exhaustion* (decreased gland function).

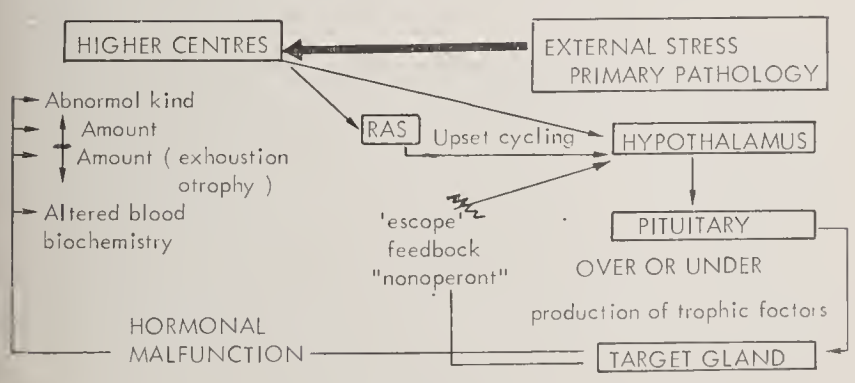

FIG. 3.
Schematic Mechanism for Etiology of Endocrine Disorders due to External, CNS—Transmitted Stress.

If we were to apply these postulates to known diseases, we could correlate the long-suspected role of psychological "shocks" in the precipitation of hyperthyroidism. Experimently it has been shown that constant electrical stimuli to the hypothalamus cause increased release of thyroid hormone.

Also this could be extended to explain a psychological origin for the onset of Cushing's disease, as, after all, the adrenal gland is the endocrine organ most intimately associated with body defenses to any stress. It has been shown that ACTH release is increased with electrical stimulation of the hypothalamus. In fact, this experiment has been extended to produce greatly increased gastric HCl secretion, indeed, causing frank gastric or duodenal ulceration and even fatal perforations in monkeys. So, we may truly have a physiological justification for the term "ulcer personality".

If we apply the third tenet of Selye's General Adaptation Syndrome, that of ultimate exhaustion, we have an explanation for idiopathic *hypofunction* of adrenal and thyroid in Addison's disease and myxoedema, after prolonged psychiatric stress.

Pitts and McClure have reported the precipitation of acute anxiety attacks by infusion of lactate. They postulated subsequently that chronic psychiatric stress leads to chronic overactivity of the C.N.S. with subsequent efferent bombardment of the adrenal medulla. This is turn leads to increased levels of adrenalin and higher than normal levels of lactate. The anxiety symptoms are produced by the feedback effects of lactate on C.N.S. function. So this is a combination of reflex hormone over-production after afferent stimuli, with behavioural manifestations due to a feedback mechanism.

In other studies, the adrenal medulla has been correlated with two personality traits, the so-called "rage in" and "rage out" types. Personalities with depressive tendencies ("rage-in") have a high level of adrenalin in the blood stream. Those who are prone to rage attacks ("rage-out") have a higher than normal level of noradrenalin. It is known that cortisol and other *cortical* hormones increase methylation of noradrenalin in the medulla. Therefore, it is postulated that chronic C.N.S. stimuli act on the adrenal cortex via the hypothalamus and pituitary to increase cortisol production; in turn increased cortisol causes increased adrenalin production and it causes behavioural and emotional changes, probably again as a result of feedback effects on the cortical and limbic systems.

A second major effect of external stresses transmitted to the endocrines, could be via a disturbance in the cycling centers in the R.A.S. (Refer to Figure 3 again.) Several illustrations warrant discussion.

Probably the best is that of acyclic anovulatory menstrual dysfunction. It is manifested by intervals of amenorrhoea or oligomenorrhoea (usually short), and

is precipitated by transient, acute psychic stresses, such as occurs in college freshies or first year student nurses. Such dysfunctional bleeding is commonly spontaneously corrected. However, as the lack of, or disrupted periods have, by themselves, psychiatric repercussions (fear of pregnancy, loss of "femininity"), gynaecologists will often resort to oral cyclic hormonal therapy, which will "reset" the R.A.S. cycling center for the reproductive system. It is interesting to speculate whether such psychic stresses similarly affect male reproductive function: here, any overt monitor is lacking.

One disease most certainly of psychiatric origin with well-studied concomitant endocrine changes is anorexia nervosa. In terms of the present model, however, it is difficult to classify. Psychogenic aversion to food leads to self-starvation and extreme inanition. The lack of appetite may be on the basis of psychological inhibition of the hypothalamic centres regulating appetite.

The most frequently noted endocrine disturbance (accompanying this condition) in women is amenorrhoea. There are two possible etiologies. Since in most cases, the amenorrhoea occurs secondarily, it is classically said to be due to starvation, protein depletion, and asynthesis of the necessary gonadotrophic, pituitary or ovarian hormones. Also, in extreme cases, there may be decreased thyroid hormone and decreased urinary steroids. This generalized endocrine dysfunction would reinforce the classical concept of the changes being caused by protein deficiency. However, in a small number of cases, the amenorrhoea *precedes* the onset of the symptoms of anorexia nervosa; so in these cases one could postulate that reticular system centers cycling appetite *and* reproductive function are inhibited and are the cause of this syndrome.

It should also be noted that obesity in women, which may or may not have psychiatric origin (e.g., agitation and anxiety leads to nervous overeating, or obsessive-compulsive reactions) frequently is accompanied by anovulatory menses, or amenorrhoea. Hypothalamic inhibition of gonadotrophins is the mechanism suspected.

In prepubertal boys there is a syndrome known as adiposogenital dystrophy, with obesity and apparently small external genitalia. It is probably due to a transient hypothalamic appetite centre disturbance. There are no concomitant endocrine chemistry disturbances, and the *apparent* small genitalia are just that—due to the abnormal amount of overlying fat. These young boys usually progress to normal, if somewhat delayed pubertal development. The important point in these cases is the use of endocrine studies, to distinguish this entity from true Froehlich's syndrome. In this latter disease, an organic cause for pituitary disturbance exists — usually a suprasellar craniopharyngioma.

II SOMATOPSYCHIC DISORDERS— PSYCHIATRIC SEQUELAE OF ENDOCRINE DISEASE

There is initially a general "giving-up" reaction which may occur in any illness—a depressive state—a sort of "overwhelmed feeling". This tends to occur just prior to the onset of acute illnesses, but is more frequently a *consequence* of chronic disease. Since the natural history of endocrine disease is long and the treatment usually prolonged, complex, and/or only incompletely successful for some, this general manifestation is to be expected. Part of the art of the physician will be to deal with it.

Secondly, the endocrine disturbance often produces marked bodily changes, such as obesity, hirsutism, masculinization or feminization. These changes tend to precipitate anxiety and depression in the unfortunate patient, due to his distorted body image, plus or minus his social ostracism. Examples where this may occur are acromegaly, giantism, dwarfism, myxoedema, Cushing's disease, Addison's disease, adrenogenital syndrome, Froehlich's syndrome and Stein-Levinthal syndrome. In such cases the role of the physician is first, by prompt diagnosis and treatment to prevent or minimize such changes; and secondly, to offer advice to treat the changes present. Such tasks require all the skill that the physician possesses.

Thirdly, however, and more specifically, there are certain psychiatric disturbances which occur because of a particular glandular dysfunction. Indeed, the psychiatric manifestations may be the *only* symptoms of the endocrine disease: therefore, it is of enormous significance for the patient to have the etiology of these *potentially curable* maladies feretted out.

In general terms, the mechanism of symptom production is one of the following two: first, too much or too little hormone *per se* affects the C.N.S., particularly the higher intellectual functions of the cortex or the limbic system; or, secondly, the C.N.S. stresses are due to metabolic imbalance (glucose, salt, water) secondary to over- or underproduction of hormones governing their homeostasis.

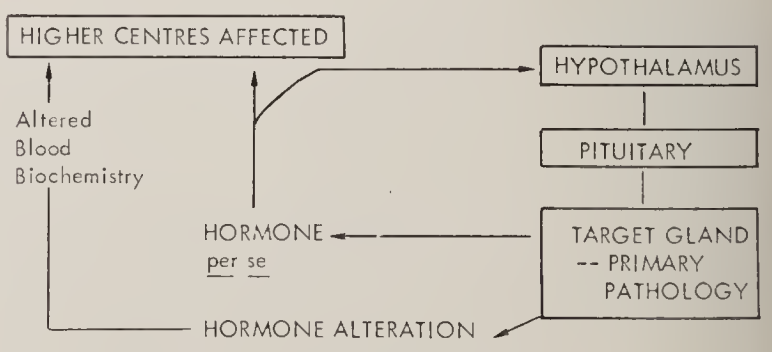

FIG. 4.
Schematic Mechanism for Etiology of Psychiatric Disorders due to Primary Endocrine Pathology.

Patients with acromegaly, for instance, exhibit psychological disturbances and emotional instability.

Hyperthyroid patients exhibit symptoms of nervousness and anxiety and they may even become psychotic. Hypothyroidism sometimes results in "myxoedema madness", which can be confused with depressive psychosis.

In hyperparathyroidism there may be depression even to the point of psychosis. Commonly in hypoparathyroidism there is anxiety, depression, increased irritability: patients may be only psychotic and not have somatic symptoms of the disease. Characteristically, these psychiatric symptoms may take a long time to diagnose, and significantly this disease is curable.

In Addison's disease there may be profound personality changes, particularly irritability and restlessness. In Cushing's disease there are also personality changes and emotional changes ranging from irritability or emotional lability, to severe depression, confusion, and frank psychoses. It is well to remember that iatrogenic Cushing's disease due to steroid therapy may also precipitate these changes.

Menopausal women frequently experience nervousness, irritability, fatiguability and lassitude. Primary treatment should include sedation and supportive psychotherapy: and if these measures fail to afford relief, estrogen replacement may be used. Hormonal changes at the menopause probably do not primarily precipitate involutional psychoses, but they certainly contribute to their onset together with psychological factors.

With hyperinsulinism, chronic hypoglycemia can lead to profound personality changes.

SUMMARY

An anatomical and physiological model of neuro-endocrine relations has been presented, with emphasis on the rôle of the reticular activating system and hypothalamus. Also proposed was a classification of *psychosomatic* endocrine diseases, due to stresses either initiated internally or transmitted from the external environment, and *somatopsychic* disorders, due to effects of derranged glandular function on the central nervous system. The probable mechanisms of production of these disorders, and certain examples of them, have been discussed.

The astute reader probably has seen the overlap of the three sections discussed. But, to salvage one's mind from a morass of confusing detail, it often is best, as in the anatomy dissection room, to pare the parts from the whole. For deeper comprehension of the concepts one should, as advocated by the physiologists, view the whole over-all. In this article, the true ramifications of neuro-endocrine relations will be appreciated by mentally super-imposing Diagrams 2, 3 and 4. But then the reader will, like Charlie Brown, cry out, "AUGH!", and revert to the simplicity, if not the sophistication of the parts!

CONCLUSION

Obviously, much of the material presented in this article is rather speculative (even though given a tentative scientific basis). It is a problem of trying to correlate the challenging specialty of psychiatry with the biochemical precision of endocrinology. The *suspicion* that they are intimately related cannot justify a scientific classification of diseases, without proof by controlled biological *in vivo* experiments. The latter are somewhat difficult to support ethically in man himself. So, comparable animal work must labour under the handicap of not reflecting the complex influences of man's psyche.

One of the oldest arguments in medicine has raged about the relative importance of genetic vs. environmental factors, i.e., biological *vs.* socio-psychological determinants, in the etiology of psychiatric disease. Hopefully, from this essay, one will see the necessity of considering *both* factors. This problem is somewhat lessened, also, if one considers the disease, either endocrine or psychiatric, within the context of the *individual* patient.

For example: why does one patient have a single episode of depression and another have a lengthy cyclical affective psychosis? The answer may be that the same socio-psychological factors act on a cycling center which is *variably susceptible* to such stresses, and the ultimate autonomy of the cycling center in the latter disorder is a repercussion of its decreased inherent *stability* in that patient.

The solution to the enigma will come only with more research into neuro-endocrine physiology, and a conscientious attempt at greater integration of biochemical endocrine knowledge and the newer psychiatric theories (such as body types, conditioning theories).

The lesson to be learned from the confusion now reigning is that, for the patient's ultimate benefit, when considering functional etiology of disease one must also rule out organic pathology. Optimistically, medical knowledge will advance to the point where a definite scientific explanation exists for such diagnostic dilemmas.

ACKNOWLEDGEMENT

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Student Research

A Biochemical Approach To Demyelination - Multiple Sclerosis

Multiple sclerosis is a common disease of the central nervous system, the etiology of which is unknown. It occurs most frequently between the ages of 20 and 40 years and has a slight predilection for females. The disease begins with a breakdown of the myelin sheath in a random fashion. Areas of white matter commonly involved are optic nerve and chiasma, pons, cerebellum and spinal cord (cervical and lumbar regions). Nerves denuded of their sheath transmit impulses, but ineffectively. With time, there is degeneration of the denuded nerve fiber, leaving sclerotic plaques within the substance of the white matter.

Epidemiological studies have shown that the disease tends to occur within certain geographical areas, in particular the moist cool areas of the temperate zones. From this knowledge Kurtze[1] and his colleagues propose that there may be an environmental factor associated with the disease, (much like soil deficient in iodine is a cause of hypothyroidism). There is a familial tendency as it can occur in more than one member of a family but it does not follow any common genetic factor. Studies have been done to try to implicate an allergic basis for the disease but to date no convincing evidence has been obtained. Viral studies have also proved unconvincing.

Other factors which are listed as possible precipitants are infection, trauma, diet, physical exertion and emotional stress.

The myelin membrane is a stable anatomical structure. Electron microscopic studies of the myelin sheath have revealed it to be a concentrically arranged layered structure (Fig. 1). In 1963, Vandenheuval[2] visualized it as a bimolecular layer of lipid sandwiched between straight chains of protein arranged at right angles to the lipid (Fig. 2). It must be emphasized that this model represents a greatly over-simplified picture of the membrane based on what was then known of the lipids present in the membrane. Virtually no information was available about the number or nature of the protein components of the membrane. It is this subject which forms the body of this article.

Chemically, the sheath is composed of lipid (80%) and protein (20%). Extensive studies made on the lipid component[3,4] have shown it to consist mainly of phospholipid, free cholesterol cerebrosides and sulfatides. There is no evidence to suggest that abnormalities in this lipid are the cause of the demyelinating process. The stability of this membrane depends on the ordered arrangement of the lipid with the protein component.

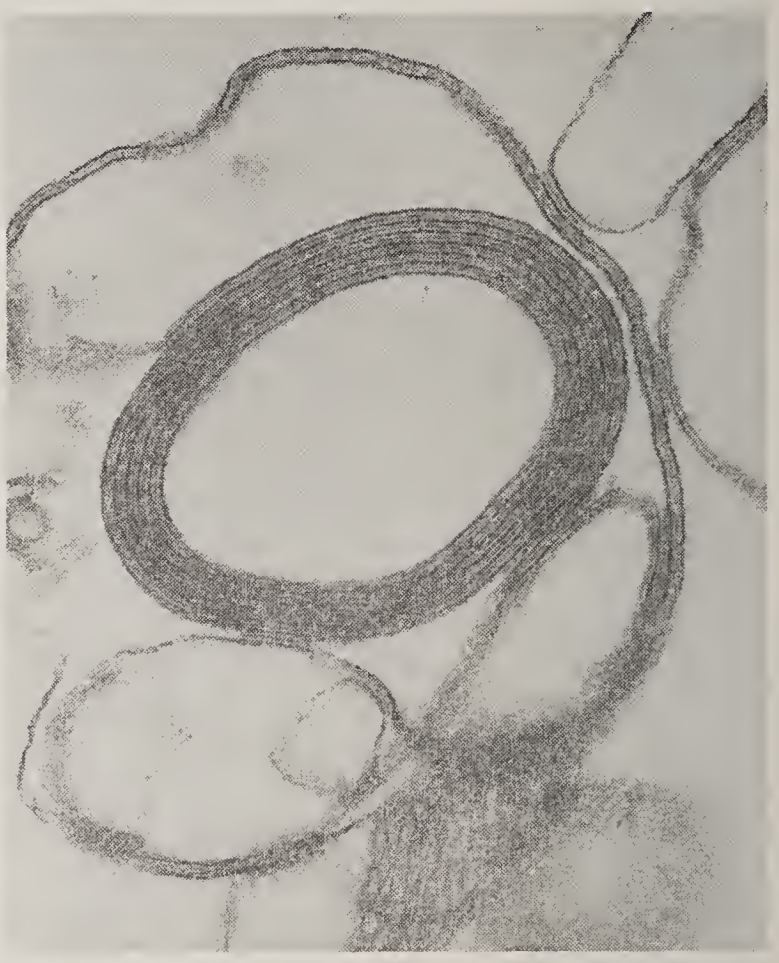

FIG. 1. Electron micrograph of myelin (x 120,000) showing a typical myelin whorl free of axonal contents.

The proteins which are closely bound to lipid have been termed "proteolipid" by Folch[5] but have not been extensively studied. Because little is known about the protein moiety, it is difficult to propose a role for it and to explain how it influences the process of demyelination.

It has been our aim to isolate and study the protein moiety of myelin from normal human brain white matter and possibly to assign a role to the protein component in the membrane. It has been well established that minor changes in a protein, such as the substitution of a single amino acid as is found in sickle cell haemoglobin, profoundly alter not only the structure of the haemoglobin but also the entire structure of the red cell membrane. Consequently, an understanding of the number and nature of the proteins in the myelin membrane may help us to understand the demyelinating process. Furthermore, if we can show that myelin proteins isolated from patients dying of multiple sclerosis differ significantly from those found in normal individuals then we may propose that these proteins (or protein) alter the entire stability of the membrane resulting in demyelination.

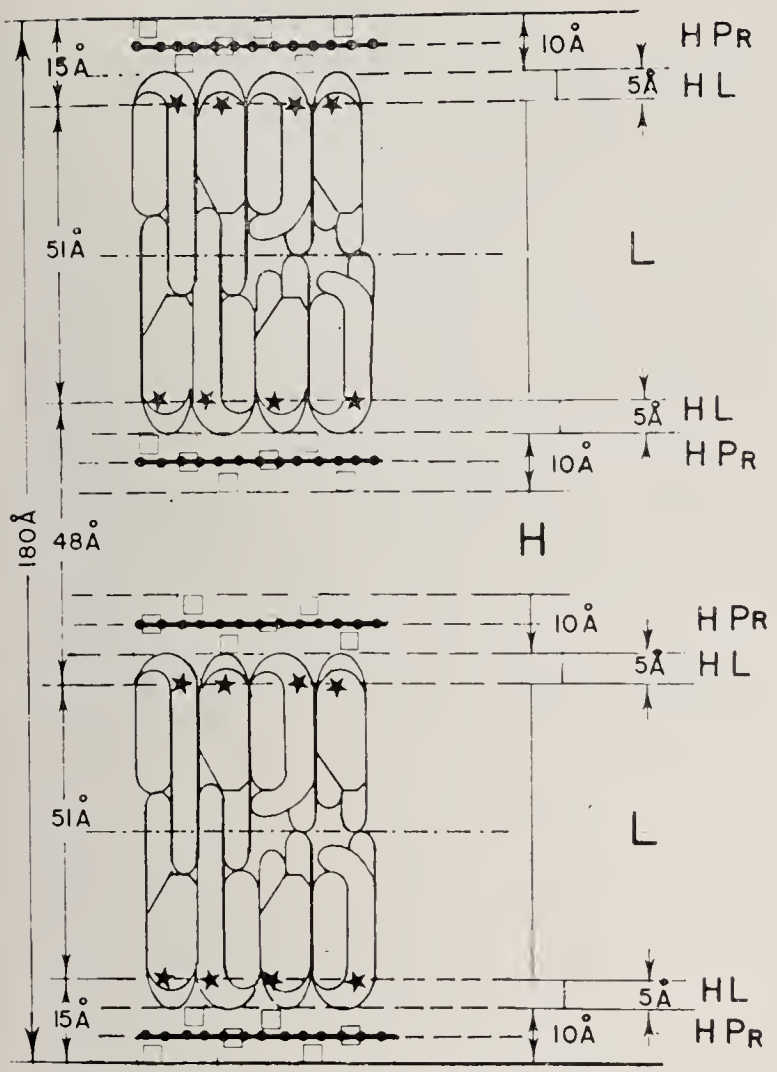

FIG. 2. Vandenheuval concept of the myelin membrane (H = Intraperiod region; L = cholesterol lipid; HL = hydrated lipid; HPr = hydrated protein) — reproduced from Vandenheuval, F. A.: Journal of the American Oil Chemists' Society, Vol. 43, No. 5, 1966.

In addition to these chemical and physical studies we have also been interested in the biological effect of myelin proteins. For this purpose it is important to have an experimental model. Experimental allergic encephalomyelitis (EAE) produced in guinea pigs by the injection of a few micrograms of myelin protein in Freund's adjuvant is such a model. Clinically, the guinea pig develops a slowly ascending paralysis beginning in the hind limbs 2-4 weeks after a single injection. Histologically, it is characterized by subcortical infiltration of leukocytes and perivascular cuffing. The encephalitogenic activity of proteins isolated from myelin will be discussed where such data are available. This experimental model is considered by many as a model of multiple sclerosis.

Myelin is isolated from human brain white matter by a subcellular fractionation procedure, employing a sucrose density gradient.[6] The purified freeze-dried myelin is then subjected to a series of chemical procedures in order to isolate the protein moiety free from the lipid moiety in a soluble workable form. So far three fractions have been isolated: a peptide fraction, a basic protein (acid-soluble) and a non-basic protein (acid-insoluble). The thioethanol-soluble peptides (TESP) and the acid-soluble protein (ASP) have been characterized quite extensively. The n-butanol-acetone insoluble protein (BAIP) has just been recently isolated and characterization is now underway. Methods of characterization include molecular weight determination, starch gel electrophoresis, determination of amino acid composition and encephalitogenic properties and high voltage electrophoresis and "fingerprinting".

Ultracentrifuge studies were performed in the Beckman Model E analytical centrifuge at 59,800 rpm. At pH 2.0, using the synthetic boundary cell, the molecular weight of the TESP was less than 2000, that of the ASP was about 10,000. Exclusion from a Sephadex G-75 column equilibrated with ammonium chloride at pH 2.0 by the method of Whitaker[7] placed the molecular weight of the TESP at approximately 1,000 and that of the ASP at approximately 10,000.

Urea-formate starch gel electrophoresis of ASP at pH 3.4 by the method of Smithies[8] revealed a single band migrating toward the cathode whereas the TESP migrated toward the cathode as a group of bands somewhat slower than the ASP. The BAIP does not migrate toward the cathode but migrates a short distance toward the anode.

In order to obtain the amino acid composition the peptides and proteins were first hydrolysed with 5.7 N constant boiling HCl at 105°C for 18 hours and then applied to a Technicon automatic amino acid analyser. Table I gives a comparison of the amino acid composition of TESP, ASP and BAIP.

It can be seen that the three fractions have quite different amino acid compositions. The most significant differences are shown in the following residues eg. cystine, which is present in BAIP, is absent from both TESP and ASP. ASP contains 24% basic residues, i.e.

$$\left(\frac{\text{arginine} + \text{histidine} + \text{lysine}}{\text{total residues}} \times 100\right).$$

TESP 19% and BAIP 14%. Other differences also exist eg. glutamic and aspartic acids.

The encephalitogenic activity of ASP, BAIP, and TESP has been determined. It was found that ASP was highly encephalitogenic, the injection of 10 micrograms being sufficient to elicit symptoms. The TESP was active but less so, requiring 50-100 micrograms. BAIP was found to be inactive at doses as high as 1000 micrograms. These data support the view put forward here that these fractions represent chemically and biologically distinct protein fractions.

The isolated fractions ASP and TESP have been compared by the fingerprinting technique so successfully applied to the haemoglobin molecule. In this technique the protein is first hydrolysed by suitable enzymes so that a number of peptides are obtained. The peptides are subjected to high voltage electrophoresis (first dimension)

TABLE I

	TESP	*ASP*	*BAIP*
Asp	2	3	2
Thr	1	2	2
Ser	2	3	3
Glu	3	3	2
Pro		4	1
Gly	2	5	3
Ala	2	3	3
Val		2	1
Gys			1
Meth			trace
Ile		1	1
Leu	1	3	3
Tyr		1	1
Phe		2	2
Lys	1	3	2
His		4	4
Arg	2	4	2

on filter paper. The strip containing the separated peptides is then sewn into another chromatographic paper and subjected to chromatography in a direction at right angles to the original electrophoretic run (second dimension).

Because the resolving power of the fingerprinting technique is so superior to other techniques when two nearly identical proteins are to be compared, one of the objectives of this work has been to compare various fractions isolated from normal brain with those isolated from patients dying of multiple sclerosis. The results of some preliminary studies indicate clear-cut differences between ASP and TESP. It is tempting to believe that a structural difference *does* exist in these protein fractions. However, only a few brains have been obtained from patients dead of multiple sclerosis and it is too early therefore, to draw definite conclusions about differences on the fingerprints. So far no fingerprinting data are available for BAIP.

The work discussed above is continuing at an accelerated pace. Other proteins may be isolated in the future. When all the protein has been isolated, it will be possible to develop a concept of a meaningful myelin membrane. Already it appears from the work presented above that two classes of protein exist in the membrane. One is largely structural (BAIP) with little or no biological function. The other may be less structural but more biologically active (ASP). It may be that demyelination may begin with a loss of the more biologically active proteins. However, at the moment this remains highly speculative.

Miss D. D. Wood, B.Sc. 6T8

ACKNOWLEDGMENT

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Recent Advances

Calcitonin

In 1961, Copp and co-workers at the University of British Columbia performed experiments on dogs in which they perfused blood high in calcium through the thyroid and parathyroid glands. This caused a prompt fall in systemic plasma calcium that could not be explained on the basis of suppressed parathyroid hormone production. As a result, they postulated the presence of a hypocalcemic factor released only from the parathyroid glands which they named "calcitonin".[1] These experiments were confirmed shortly thereafter by MacIntyre and his associates in London, England.

The discovery of "thyrocalcitonin" in 1963 by Hirsch, Gauthier, and Munson[2 3] grew out of an investigation of the greater fall of serum calcium levels in rats after parathyroidectomy by hot wire cautery than by surgical excision. They found that the differential effect could be explained by a cautery-stimulated release of a hypocalcemic substance (thyrocalcitonin) from the thyroid gland into the circulation. Copp's "calcitonin" was renamed "thyrocalcitonin" by these scientists because of its thyroid, rather than parathyroid, origin.

Thus, the recent discovery of calcitonin has sparked an enormous amount of research into its physiological importance as a hormone, and into its possible application to clinical medicine.

CHEMICAL PROPERTIES OF CALCITIONIN

Haymovits and Rosen working with human thyroid glands obtained from cadavers after accidental death and devoid of gross pathological change, found human calcitonin to be a polypeptide with a molecular weight in the range of 5,000 - 8,000.[4] Because of the much greater availability of pig calcitonin, much experimental work has been done on it. Although immunologically it differs from human calcitonin,[5] it appears to be physiologically active in man.[6]

SOURCE OF CALCITONIN

Calcitonin has been found in the thyroid gland of man, pig, rabbit, guinea pig, dog, goat, ox, and monkey.[5] Munson's group was the first to show the presence of calcitonin in human thyroid tissue. Agreement has been reached that the source of calcitonin is the thyroid parafollicular "C" cells which arise from the embryonic ultimobranchial bodies.[2 3 7-10] The ultimobranchial glands are found in all vertebrates, except cyclostomes, and they develop from the last branchial pouch in much the same position as the parathyroids which develop from the third and fourth branchial pouches. In mammals, the ultimobranchials merge with the thyroid.

The "C" cells may be recognized by specific histochemical techniques, and have been shown in all mammalian thyroids studied.[2]

ACTIONS OF CALCITONIN

In the following discussion, it should be remembered that up to the present day, most of the research with regard to calcitonin has been performed on animals, rather than humans. But those studies which have been performed on humans correlate well with the findings in animals.

There is broad agreement that the major biologic action of calcitonin is inhibition of bone resorption.[2 3 7 9 11] This results in a decreased release of calcium and phosphorus into the blood; hence calcitonin lowers blood levels of calcium *and* phosphorus. Calcitonin also inhibits the destruction of the insoluble, mature collagen of the bone matrix as evidenced by a reduction in the urinary excretion of hydroxyproline, a component of bone collagen.[7] (Urinary hydroxyproline is a good index of the activity of bone breakdown).[2]

The evidence indicates that some process other than inhibition of secretion, inactivation, or competitive inhibition of parathyroid hormone at its site of action* must be involved in the mechanism of action of calcitonin.[3 7] The anterior pituitary gland has also been shown not to be an essential mediator of the action of calcitonin.[3]

Although calcitonin negates the action of parathyroid hormone on bone resorption, it does not suppress the action of parathyroid hormone on either the kidney or gastrointestinal tract,[3 11] nor is there evidence that calcitonin has an independent effect on either of these latter organ systems.[5]

Because calcitonin lowers blood calcium and decreases the release of hydroxyproline from bone collagen, and apparently may not affect other organ systems, there is also a concomitant decrease in the urinary excretion of calcium and hydroxyproline.[11] However, there is disagreement concerning the effect of calcitonin on phosphorus excretion.**

*It should be remembered that parathyroid hormone increases bone resorption (a completely opposite effect to that of calcitonin) resulting in the release of calcium, phosphorus, and hydroxyproline from bone into the blood stream. It also increases absorption of calcium from the gut in the presence of vitamin D and decreases renal tubular reabsorption of phosphorus.

**MacIntyre and associates, in experiments on rats, have postulated that calcitonin acts on the kidney to increase phosphorus excretion.[12] Most other workers in the field feel that calcitonin has no direct effect on the kidney.[7 9 11 12]

Since bone remodelling represents the proper balance between bone formation and bone resorption and is necessary to ensure the proper growth and maintenance of the skeleton, it is tempting to speculate that calcitonin is a hormone involved in bone remodelling.

It would appear that the sole factor responsible for regulating the release of calcitonin from the thyroid gland is the level of plasma calcium. With proof of the direct action of calcitonin on bone, the following hypothesis becomes reasonable. When hypercalcemic blood reaches the thyroid it stimulates the parafollicular or "C" cells of the thyroid gland, which store calcitonin, to secrete more of the hormone. The released calcitonin acts to inhibit bone resorption. Consequently, less calcium is released from bone into the blood stream per unit time. The end result is a reduction of the blood calcium to normal, removing the stimulus for increased secretion of calcitonin.[3 5]

CLINICAL ASPECTS OF CALCITONIN METABOLISM

Although no disease entity in humans has definitely been linked to calcitonin metabolism, there is some evidence that calcitonin may be associated with certain disease states. Of special interest was the finding of 100 times the normal concentration of calcitonin in thyroid specimens from two human cases of pseudohypoparathyroidism, leading to the suspicion, that an abnormality in calcitonin metabolism may have contributed to the patients' persistent hypocalcemia.[5]

Calcitonin may in the near future be an important therapeutic agent in certain disease states. Foster and co-workers have used pig calcitonin to lower serum levels of calcium in three patients with hypercalcemia associated with osteolytic bony metastases.[6] Haymovits and Rosen have administered a dose of 15 mg. of human calcitonin in an intravenous infusion for 60 minutes to 2 adult patients with hypercalcemia, and this resulted in a sustained reduction of serum calcium (by about 2 mg./100 ml.) and phosphorus lasting about 3 hours.[4] Calcitonin should therefore be tested for its usefulness in the treatment of other conditions in which hypercalcemia or a negative calcium balance may be important features. Hyperparathroidism, hypervitaminosis D, a tendency to form kidney stones, forced immobilization, weightlessness in astronauts, and osteoporosis are obvious examples.

SUMMARY

Calcitonin and parathyroid hormone are antagonistic in their effects on plasma calcium levels. Calcitonin is active in the absence of parathyroid hormone and its effect is not dependent on the presence of the pituitary gland, kidney, or gastrointestinal tract. It acts directly on bone *in vitro* to inhibit resorption.

In the absence of the thyroid gland, recovery from induced hypercalcemia is slower than normal, and this deficiency can be corrected by giving calcitonin. However, a more important function of calcitonin in normal physiology other than protection against hypercalcemia may be its role in the development and maintenance of the skeleton.

Much is yet to be learned regarding the possible diagnostic (eg., levels of calcitonin in human plasma) and therapeutic benefits of calcitonin but its future in clinical medicine appears bright.

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Fundamentals Of Radiologic Examination

The Urinary Tract

In this article it is the intention of the author to outline briefly the more routine radiologic methods of examination of the urinary tract. Following this is a discussion of the more common urinary tract lesions, and their radiologic appearance.

A. METHODS OF EXAMINATION

1) The Plain Film of Kidney, Ureter and Bladder (KUB)—See Fig. 1A

It is imperative that the plain film be made prior to the Intravenous Pyelogram (I.V.P.). Radio-opaque calculi can be seen clearly on the plain film. These *may* disappear if contrast media is allowed to surround them, thereby causing confusion in interpretation. Once again, a routine method of examination is essential. Initially, attention is focused on the outlines of both kidneys which may or may not stand out clearly on the K.U.B. Size, position and contour (to be discussed below) are especially noted. Both renal and ureteral areas are carefully scrutinized for the presence of radio-opaque calculi. The spinal column and the psoas muscle shadows are observed. Scoliosis of the spinal column, obliteration of the normal psoas shadow, or both, may be suggestive of perirenal inflammation such as a perinephric abscess. The region of the sacrum must be examined carefully as small calculi may be overlooked when they overlie bone. The bladder region is closely examined for calculi and phleboliths. Phleboliths are concretions in a vein resulting from the calcification of an old thrombus. They are small, round, regular and doughnut-shaped, usually appear below the ischial spines, and therefore should not be confused with the more irregular ureteral calculi.

Soft tissue shadows in the abdomen may be due to normal anatomical structures like kidney, spleen, liver and gall-bladder. However, pathological soft tissue shadows also appear: for example, massive hemorrhage, retroperitoneal tumors or an extensive inflammatory process in and around a kidney may appear in the plain film as a large, diffuse area of increased density sometimes involving almost the entire half of the abdomen and obliterating the normal outline of the abdominal organs on the involved side.

Soft tissue shadows in the pelvic region may be due to the normal outline of the urinary bladder (which may be visualized when filled with urine) or pelvic tumors in women. A more detailed discussion of the *opaque* urinary and extraurinary shadows follows below.

2) Intravenous Pyelogram (I.V.P.)

This procedure involves intravenous injection of contrast media (Hypaque or Renograffin). Immediately before injection of the contrast medium, the patient voids. If this is not done, the diffusion of contrast medium in a urine-filled bladder may produce a cystogram of sufficient size and density to obscure the lower parts of the ureters. A plain film is then taken. Following this, the contrast medium is injected into a suitable vein in the antecubital fossa or back of hand. The first film is exposed 5 minutes after the injection. Subsequent films are taken at 10 minutes, 20 minutes and after voiding. In the case of poor renal function or advanced stasis (hydronephrosis and hydroureter) much later exposures are required to provide adequate visualization. In complicated cases, when the kidneys are not concentrating well (which is usually reflected by decreased renal function, and a BUN greater than 30 mg. %), the I.V.P. may not show up well. In some such cases, an *infusion pyelogram* is done, in which a larger than normal amount of contrast medium is infused over a period of time rather than by bolus injection as in the normal I.V.P. Two other techniques known as: 1) *urea washout pyelography* and 2) *timed pyelography* were discussed by P. Tepperman in The Current Status of Renal Hypertension in the first issue this year. The reader is referred to his paper.

Indications and Advantages

a. Visualization of the upper urinary tract without the uncomfortable cystoscopic examination.

b. When urethral catheterization is impossible, e.g. marked enlargement of the prostate gland.

c. Recognition of injury to the urinary tract following accidents or surgery.

d. Detection of developmental anomalies e.g. duplication of the ureter.

e. A patient presenting with hematuria.

Disadvantages and Contradictions

a. Incomplete visualization and poor detail due to overlying gas and feces.

b. Previous allergic reactions to I.V.P. contrast media.

c. When the BUN is greater than 30 mg. %, the contrast medium is not excreted in sufficient concentration for visualization unless double doses or an infusion pyelogram are used. Using large enough doses, the kidneys can be visualized up to a BUN of 100 mg. %.

d. Patients with thyrotoxicosis—because the iodine-containing contrast agent invalidates the PBI.

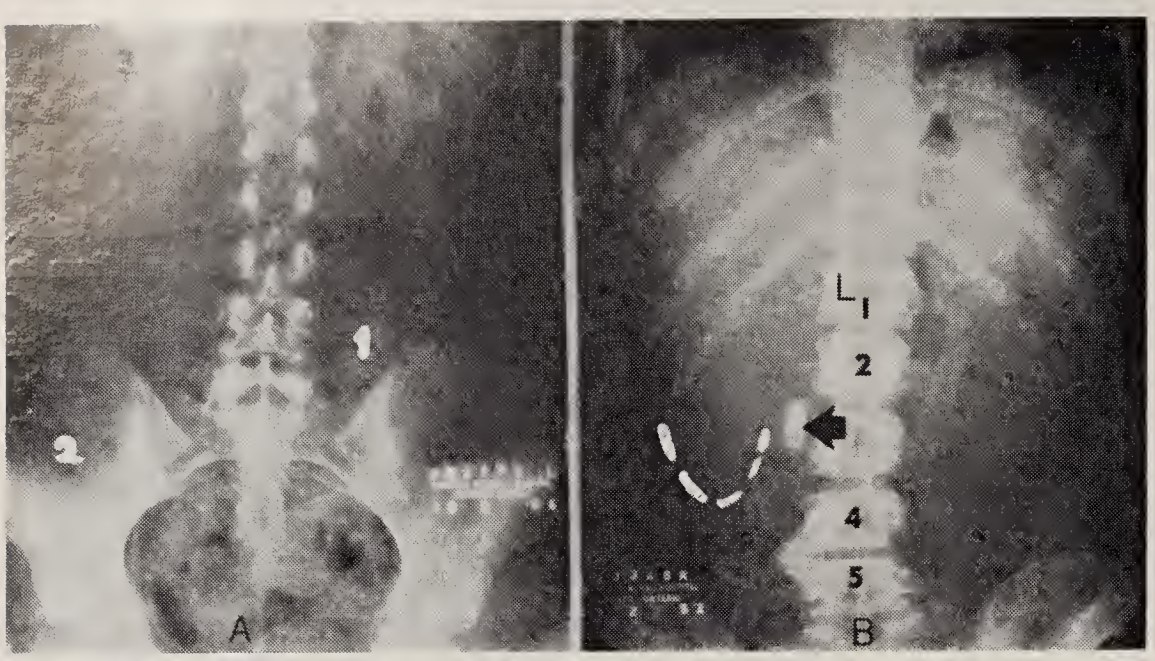

FIG. 1.

(A) Normal Plain Film (KUB) with poor visualization of the kidney shadows.
1. Psoas Muscle Shadow
2. Gas in Cecal Region
3. Region of Liver

(B) Case 1 — See text of article.

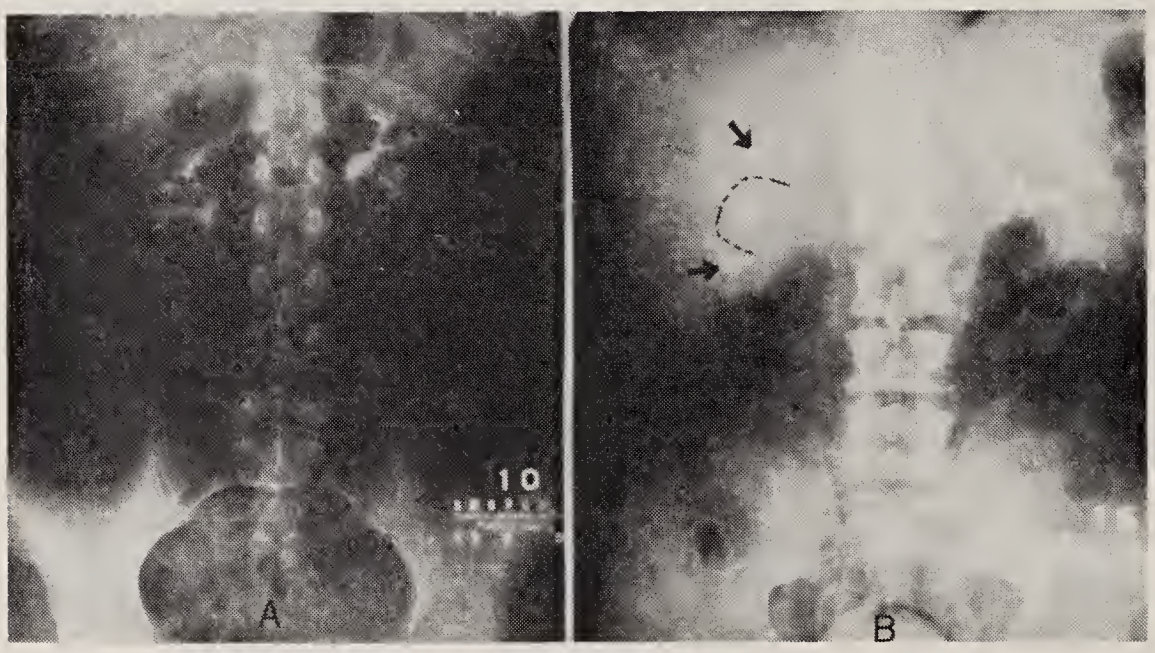

FIG. 2.

(A) Normal 10 minute I.V.P. showing well defined outlines of calyces and pelves, and partial filling of the ureters.

(B) Case 2 — See text of article.

Radiologic Appearance of a Normal I.V.P.—See Fig. 2A

Kidney—The average kidney is approximately 12 cm. long. The kidneys extend from the 11th interspace to the 3rd lumbar vertebra about 2 inches from the midline at the hilum. The left kidney is usually ½ inch higher than the right. The kidneys are symmetrical in shape and their outlines are smooth.

Renal Pelvis—This structure is usually triangular in shape with the base of the triangle parallel to the long axis of the body. However, a wide range of shapes may occur such as square pelves, and occasionally oval and globular pelves. Incomplete filling of a normal pelvis and calyceal system is also capable of producing unusual configurations which may be incorrectly diagnosed as pathologic lesions; in such cases, with better filling the pyelogram will appear normal.

Calyces—At least 3 and sometimes 4 or more major calyces should be seen. The minor calyces arise from the terminal portions of a major calyx. The number of minor calyces arising from each major calyx is quite variable. It is extremely important to look carefully at the tips (fornix) of each minor calyx. Each should terminate in a sharp point (Fig. 2A). Obliteration of the normally sharply defined minor calyceal outline is highly suggestive of a pathologic lesion. In the usual I.V.P., not all of the minor calyces are clearly outlined, some appearing more or less rounded in shape. This is probably due to incomplete filling, over-distention, or a minor calyx seen 'end on'. Comparison with the calyceal system on the opposite side often helps to determine whether a suspected lesion is of pathologic significance.

Ureters—The ureters begin at the renal pelvis, pass downward over the tips of the transverse processes to reach the pelvic brim (over the sacro-iliac joint), pass laterally to almost reach the pelvic sidewall, and then swing medially and forward into the bladder. The various parts of the ureter are not uniform in diameter. There are 3 main points of narrowing.

1. Ureteropelvic junction
2. Ureterovesical junction
3. As the ureter crosses the pelvic brim.

Therefore, it is important that the appearance of narrowing or dilatation be of fairly marked degree before it is interpreted as being abnormal. Incomplete filling defects and apparent narrowing of the ureters are quite commonly due to peristalsis.

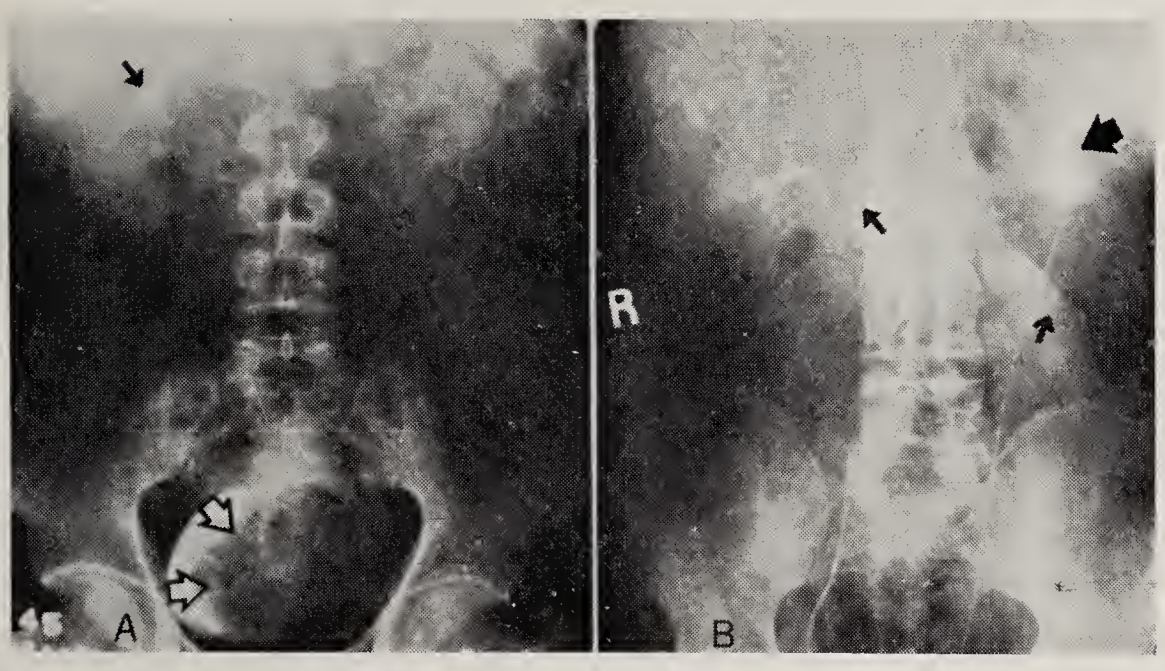

FIG. 3.

(A) Case 3 — Large filling defect in urinary bladder. See text of article.

(B) Case 4 — See text of article.

Kinks—and apparent strictures of the ureter are considered normal unless one can demonstrate dilatation of the ureter or pelvis above the point of narrowing.

Bladder—The bladder should be seen to fill well on the later films and should empty well after voiding.

3) Retrograde Pyelography

This requires that catheters be introduced through a cystoscope into the ureters and renal pelves. Care must be taken to prevent trauma to the ureters which will result in spasm. The 20-30% Hypaque is then injected. Usually 5-10 c.c. is sufficient. After 4-5 c.c. of contrast medium has been injected the catheter is withdrawn 2 inches and the injection is continued, to allow the ureter to fill. The films are taken the moment the injection is stopped.

Advantages and Indications

1. Casts a dense shadow and in most cases will outline calyces, pelvis and ureter in *one film*.

2. Excellent detail despite gas or fecal material in the bowel.

3. Detects moderate degrees of stasis in the renal pelvis and ureter.

4. When renal function is reduced to the extent that there is no visualization using I.V.P.

Disadvantages and Contradictions

1. Discomfort and pain to patient.

2. May induce spasm of ureters and calyces from trauma.

3. May produce colic, fever and rarely an acute cortical infection. The details of the structures outlined by this method have been discussed above.

Other special methods of urographic examination include:

Cystography and Cystourethrography
Renal Arteriography
Nephrotomography
Fluoroscopy.

These are beyond the scope of this article. The first two will be briefly discussed in next month's journal.

B. CALCULI OF THE URINARY TRACT

1. Radio-opaque calculi

These comprise approximately 90% of all urinary calculi and consist of calcium oxalate, calcium phosphate or a mixture of both.

One suspects a urinary calculus in the plain film when a calcific shadow overlies the areas where the kidneys, ureters and bladder are normally situated. In the case of renal calculi it is often possible to determine the location of the stone if it has assumed the shape of a terminal calyx or formed a cast of the pelvis and calyces (Staghorn calculus). Other types of renal calculi, however, require an I.V.P. to establish their position. If there is insufficient visualization even with an I.V.P., then a retrograde pyelogram is indicated. These procedures are employed to rule out confusing extraurinary shadows like calcified costal cartilages, in addition to elucidating the position of a calculus. Ureteral calculi most commonly are located either at the ureterovesical or ureteropelvic junctions, and produce dilatation of the urinary tract above the point of obstruction. Difficulties in diagnosis of ureteral stones arise when they are of small size and when they are obscured by gas or the bony structures which they overlie. Phleboliths and small calcified lymph nodes along the course of the ureter may be sources of error in diagnosis. Therefore I.V.P.'s, and if required retrograde studies, must be utilized when ureteral stones are suspected. The causes of opaque calcium stones include primary and secondary hyperparathyroidism, idiopathic hypercalcuria, sarcoidosis, hyper-vitaminosis D, milk-alkali syndrome, malignancy (bronchogenic carcinoma), renal tubular acidosis, acromegaly and Cushing's syndrome. In addition to calculi, generalized calcification in a kidney or ureter, or both must be looked for in every roentgenogram. This appears in a variety of conditions the most important of which are hyperparathyroidism, multiple

myeloma, tuberculosis, chronic pyelonephritis, renal tumours and calcified cysts.

2. Non radio-opaque calculi

These comprise approximately 10% of urinary calculi and consist of uric acid, cystine and xanthine stones. If these stones are small they may be impossible to demonstrate. If of sufficient size, they may be visualized as radiolucent shadows or filling defects, during a retrograde pyelogram (for renal non-opaque stones) or an I.V.P. (for ureteral non-opaque stones). Most calculi in the urinary bladder are relatively non-opaque and are best diagnosed by means of cystoscopy.

3. Radiologic Findings

The most common condition produced by a calculus is obstruction. Any cause of obstruction (stone, ureteral stricture or stenosis, tumor, ureterocele etc.) will produce dilatation proximal to the site of obstruction. Thus, dilatation of the ureter (hydroureter), or pelvis and calyces (hydronephrosis), or both, may develop depending on the position of the obstruction. Obstruction, of course, predisposes to infection which is usually quite easily recognized on pyelograms. Stones in the renal pelvis usually produce hydronephrosis, but may cause spasm and contraction of the pelvis rather than dilatation. In such cases, on the I.V.P. the pelvis is seen tightly contracted around the stone, with an associated contraction of the ureteropelvic junction. Obstruction in the ureter produces in sequence widening, lengthening and tortuosity of the ureter (hydroureter) above the obstruction (in addition to hydronephrosis). If infection is present, however, there also may be dilatation below the obstruction.

C. INFECTIONS OF THE URINARY TRACT

1. Chronic Pyelonephritis

This is usually a bilateral disease although unilateral pyelonephritis can occur. It is a destructive process with a tendency to scarring and retraction of the renal papilla. Using I.V.P.'s and retrograde pyelograms, early changes can be seen. The involved kidney is often greatly reduced in size. However, it is a patchy, assymetrical (irregular in outline) reduction in size, as contrasted to the symmetrical reduction in size in the kidney of chronic glomerulonephritis. These two conditions are impossible to differentiate in the end stage kidney. There is clubbing, blunting, and distortion of the calyces associated with varying degrees of dilatation of the renal pelvis. These changes are due to the irregular scarring and retraction of the renal papillae. It is important to realize that accompanying the calyceal changes there is irregular thinning and narrowing of the renal parenchyma. That is, the distance between the involved calyx (calyces) and the kidney outline is greatly reduced so that in severe cases, the calyces appear to lie almost beneath the renal capsule. It is apparent from the foregoing that adequate visualization of the renal outline is extremely important. Unfortunately pyelographic studies do not always produce distinct renal outlines and therefore one must resort to the use of nephrotomograms to overcome this problem.

Changes in the ureter occur simultaneously with those in the pelvis and calyces; however, they are not usually apparent until the disease is moderately advanced. The changes consist of irregular regions of dilatation and constriction usually accompanied by tortuosity.

2. Tuberculosis of the urinary tract

This is most commonly a secondary disease that results from the hematogenous dissemination of tubercle bacilli from a primary focus usually in the lungs, bones or joints. Radiologically, the plain film is examined initially. The more important radiological findings consistent with T.B. are irregularity or enlargement of the soft tissue shadow of the involved kidney, indefinite and irregular cortical calcifications overlying the kidney, and occasionally calcific shadows overlying ureters and bladder. Associated tuberculous lesions of the bony structures, psoas muscle, and of course the lungs may be seen on plain films. Renal calcification is by no means pathognomonic of T.B. It may occur as well, as the end result of almost any non-tuberculous infection and in the conditions already discussed. Utilizing I.V.P.'s and retrograde examinations, the commonest changes found in urinary T.B. are:

1. Absence or delay in visualization.
2. Variable degrees of dilatation and retraction of the calyceal system due to the invasion of the tubercle bacilli into the renal pyramids.
3. 'Moth-eaten' outline of calyces due to erosion of pyramids and cortical necrosis.
4. Calyceal isolation and eventual obliteration.
5. Dilatation and eventual obliteration of the renal pelvis outline.
6. As a result of the tuberculous inflammatory process, the ureter may become thickened and lose its elasticity and therefore, areas of fibrosis and constriction may alternate with areas of inflammatory dilatation.

D. RENAL CYSTS AND TUMOURS

1. Simple Cysts

These arise from the renal parenchyma usually near the periphery and tend to grow away from the kidney. Thus the plain film may show a smooth outlined, round shadow of the cyst, usually overlying the upper or lower pole. However, a tumour may present exactly the same way, making diagnosis extremely difficult. Renal cysts often show varying amounts of calcification as well. The deformity seen on I.V.P. or retrograde examination depends on the position of the cyst. When the cyst is located in the periphery, the renal pelvis and calyces may not be deformed. When it lies deeper within

the kidney parenchyma the calyces and pelvis may be considerably distorted, often simulating the appearance of an expanding lesion such as a neoplasm. The distorted calyces may be flattened, dilated, obliterated, displaced, or crescentic in outline.

2. Renal Cell Carcinoma (Hypernephroma)

This tumor occurs twice as frequently in males as in females and usually presents with symptoms such as hematuria or vague flank pain.

The plain film may show enlargement of the kidney and/or irregularity or obliteration of the renal contour. These findings must be further clarified using I.V.P. and retrograde examinations. The latter procedures often reveal one or more of the following:

(a) elongation or distortion of one or more calyces often presenting the appearance of an expanding intrarenal lesion.

(b) obliteration and thus, non visualization of portions of the calyces, so that irregular, detached patches of contrast medium are all that can be seen.

(c) complete calyceal obliteration.

(d) encroachment on the renal pelvis causing flattening, narrowing, irregular filling defects, dilatation, or complete obliteration.

(e) calcification of a long-standing tumor simulating the appearance of a renal cyst.

(f) abnormal position of the renal pelvis.

It is evident from the foregoing that cysts and tumors may be easily confused. When the slightest doubt does exist one should attempt to clarify the issue using:

1. Nephrotomograms to clearly see the renal outline.
2. Arteriography to show the presence or absence of tumor vessels. (Tumor 'blush').

CASE HISTORIES

Case No. 1 (FIG. 1B)

A 35 year old woman presented with fatigue and a 35 lb. weight loss over an eighteen month period. Her past history included an attack of renal colic four years previously. A large tender right kidney was found on physical examination. The plain film shows an enlarged right kidney shadow with dense irregular calcification along the course of the upper ureter. A subsequent I.V.P. showed no function on the right side. Retrograde examination revealed obstruction of the upper ureter by a calculus at the uretero-pelvic junction with only a little dye being able to get above the obstruction. At operation a huge pyonephrosis with a stone at the uretero-pelvic junction was found.

Case No. 2. (FIG. 2B)

A 54 year old male was admitted to hospital following two days of crampy abdominal pain and hematuria. The 15 minute I.V.P. film shows a centrally located lesion in the right kidney. The calyceal system on the right side appears grossly deformed (arrows) and compressed when compared with the normal calyceal system on the left side. This deformity is considered to represent a cyst or tumor. Subsequent arteriography showed increased vascularization of the entire kidney and the diagnosis of hypernephroma was made. However, at operation a large intrarenal retention cyst with pelvic compression was found.

Case No. 3. (FIG. 3A)

A 60 year old male presented with several episodes of hematuria over the past ten years. Four days prior to admission constant hematuria developed. The physical examination was not remarkable. The plain film of the abdomen showed scattered flecks of calcium in the region of the urinary bladder. The 45 minute I.V.P. film reveals a polypoid lesion originating from the left side of the urinary bladder and almost entirely filling its cavity. There is in addition, some obstruction of the right ureter as evidenced by the dilated right calyceal system (arrow). Cystoscopy revealed a fungating bladder tumor which was removed at operation. The final pathological diagnosis was transitional cell carcinoma of the bladder.

Case No. 4. (FIG. 3B)

A 48 year old male presented with a history of left flank pain and low back stiffness of one year's duration. Urinalysis and microscopic revealed no albumin, 2-3 WBC/HPF and 1-3 RBC/HPF. Acid fast bacilli were found in the bladder and the urine from the left kidney. The retrograde pyelogram shows complete obliteration of the normal calyceal and pelvic outlines and their replacement by a ragged pelvic cavity. Note the destruction of the disc spaces at the T_{12}/L_1, and L_2/L_3 levels. Also note the large left psaos abscess. The final diagnosis was tuberculosis of the left kidney and the spine with an associated tuberculous abscess in the left psoas muscle.

Z. Cohen 6T9

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Clinicopathological Conference

Intractable Congestive Heart Failure In A 51 Year Old Male

CASE PRESENTATION

A 51 year old male was admitted to hospital for assessment of his cardiac status on November 8, 1966. He had a history of increasing shortness of breath on climbing hills for approximately two or three years and in July of 1966 he noticed the onset of shortness of breath with much less exertion. Shortly thereafter he developed squeezing restrosternal pain that radiated down his left arm. This was provoked by exertion, relieved by rest, and it generally lasted five to ten minutes.

These pains were present for approximately one month and following this he began noticing shortness of breath on minimal exertion, abdominal swelling, and swelling of his ankles. He was admitted to hospital in Georgetown and given Digoxin and diuretics, and following treatment he felt better. However, over the three week period in hospital he did not improve as he felt he should and therefore was transferred to the Toronto General Hospital for further investigation and treatment.

The history of present illness at the time of admission to hospital included palpitations, two-pillow orthopnea, and occasional episodes of paroxysmal nocturnal dyspnea. There was no history in the past of hypertension, myocardial infarction, or rheumatic fever.

The history of past health was non-contributory: family history revealed that his father died at age 72 of a heart condition, a brother died at age 11 with anasarca (aetiology not recorded), his mother died at age 61 from carcinoma, and he had three sisters all alive and well.

On physical examination he was noted to be diffusely pigmented and in no acute distress. The head and neck were normal. Examination of his chest revealed small bilateral pleural effusions and a few fine basal rales bilaterally. Examination of the cardiovascular system: the heart rate was 96 per minute and regular and the blood pressure 100/70. The jugular veins were distended 15 cms. above the sternal angle of Louis at 45 degrees. Both a and v waves were present and these were equal in height. There was a rapid x descent and venous pressure decreased on inspiration. There was no pulsus paradoxus. The cardiac apex was palpable 13 cms. from the midclavicular line in the 6th intercostal space. There was no right or left ventricular heave. The first and second heart sounds were decreased in intensity. A normal physiological split of the second sound was heard, and a diastolic gallop was present. There was bilateral 3+ edema of the legs to the knees. The peripheral pulses were palpable and no bruits were heard.

Examination of the abdomen revealed diffuse tenderness and minimal ascites; the liver was palpable 9 cm. below the right costal margin and the spleen 3 cm. below the left costal margin. The neurological examination was within normal limits.

Laboratory investigation revealed the following: hemoglobin 13.6 gms., WBC 6.900, differential—neutrophils 61%, lymphocytes 37%, monocytes 2%. The E.S.R. was 16 mm. The smear showed macrocytosis, anisocytosis and mild poikilocytosis. Platelets were normal.

The urinalysis revealed a random specific gravity of 1.011, trace protein, sugar negative, hemostix positive; on microscopic examination there were 2 to 5 rbc/hpf. BUN was 36 - 40 mg.%, FBS 86 mg.%, Na 143 mEq/L, K 3.9 mEq/L, Cl 99 mEq/L, CO_2 content 30 mEq/L. Prothrombin time was 13 seconds. Serum cholesterol was 258 mg.%, calcium 9.8 mg.%, and phosphorus 4.1 mg.%. A serum protein electrophoretic strip revealed a total protein of 6.5 gm.% with 48% albumin, and 52% globulin. The globulin was made up of 6% alpha 1, 16% alpha 2, 16% beta and 14% gamma globulin. P.B.I. was 5.7, T-3 sponge resin uptake 30%, and I^{131} uptake 17%. Serum iron was 45 mcg.%, iron-binding capacity 297 mcgs.%, and saturation 15%. Twenty-four hour urine protein was 1.6 gms. Screening test for 5-H.I.A.A. (5-hydroxyindole acetic acid) was negative. Several L.E. cell tests were negative. Latex fixation was negative. A congo red test showed absorption after 30 minutes of 34%. A biopsy of the gingiva was within normal limits. Chest X-ray revealed a cardiac size within the upper limits of normal. Fluoroscopy showed that the heart contracted poorly and a right pleural effusion was noted. An E.C.G. showed normal sinus rhythm, a low voltage and generalized T wave flatness with some negative T waves, indicative of diffuse myocardial damage. Repeat E.C.G. showed sinus and nodal rhythm with ventricular premature beats but no significant change.

COURSE AND TREATMENT IN HOSPITAL

The patient was treated with a 400 mg. sodium diet, Digoxin and Lasix. However, in spite of this his failure remained resistant to treatment. The BUN rose to 72 mg.%, and the serum creatinine to 3.5 mg.%; his creatinine clearance dropped to 18 cc. per minute. The P.S.P. at this time revealed only 3.8% excretion in 15

FIG. 1. AP view of the chest showing left ventricular and right atrial enlargement.

minutes and 23% excretion after 120 minutes. In spite of intensive therapy for his heart failure the patient became progressively more edematous and short of breath, and died 28 days after admission to hospital.

DIFFERENTIAL DIAGNOSIS

The history was given to Dr. E. D. Wigle, of the Toronto General Hospital, and his discussion of the differential diagnosis follows:

DR. E. D. WIGLE:

This 51 yr. old male presents with a history of progressive heart failure that was unresponsive to treatment. In approaching the problem of heart disease of unknown etiology, one must consider "secondary" causes of heart disease and those causing primary myocardial disease —the cardiomyopathies.

In the former are grouped congenital, hypertensive, rheumatic, and arteriosclerotic heart disease, primary pulmonary hypertension, constrictive pericarditis or pericardial effusion, syphilis, cor pulmonale and the high cardiac output states such as anemia, beriberi or thyrotoxicosis.

Hypertensive, rheumatic and congenital heart disease are unlikely causes because of a blood pressure within normal limits, no history of rheumatic fever and no murmurs on auscultation.

Considering constrictive pericarditis as a possible cause, it is worth noting that pronounced congestive hepatomegaly, ascites and dependent edema are always demonstrable. In about half the patients the heart is normal in size with distant heart sounds. The basic abnormality is the inability of the ventricles to fill adequately during diastole because of the limitations imposed by the rigid, thickened pericardium. A Küssmaul sign and pulsus paradoxus are the clinical signs elicited in this condition. Both were absent. However, the edema, and liver enlargement do not rule out pericarditis. Primary pulmonary hypertension (i.e. without any obvious cause) may be inferred if there is accentuation of the pulmonary second sound, enlargement of the pulmonary artery and right ventricular hypertrophy. The chest X-ray showed a heart within normal limits (cardio-thoracic ratio 5.8 cm./11.1 cm.), and no demonstrable enlargement of the pulmonary arteries (Fig. 1). Both heart sounds were decreased and some right ventricular and left atrial hypertrophy noted.

The principle causes of chronic cor pulmonale are emphysema and diffuse fibrosis. Less frequently the condition results from obstruction in the pulmonary artery or arterioles from thrombo-embolism. Nothing in this patient's history or physical examination suggests chronic lung disease; small bilateral pleural effusions and a few fine basal rales are signs of heart failure. The chest X-ray was normal otherwise, and showed no areas of hyperlucency or fibrosis.

Investigation for anemia and thyrotoxicosis as a possible cause was carried out. Hemoglobin, serum iron, iron binding capacity and saturation were normal; similarly, thyroid function tests were within normal limits.

This leaves arteriosclerotic heart disease as a possible etiological agent in this man's heart failure. The anginal pains however, are atypical in that they occurred subsequent to the shortness of breath that had been present for two to three years. No evidence of myocardial infarction was demonstrated on the ECG and with no cardiomegaly, arteriosclerosis would be unlikely.

In those conditions known to produce primary myocardial disease, 75 percent are idiopathic, and 25 percent a discrete entity. A clinical classification of such conditions that affect the myocardium includes obstructive, congestive, or restrictive causes. In obstructive cardiomyopathy, such as subaortic muscular stenosis, there is sufficient constriction to produce a systolic murmur, a forceful left ventricular impulse or a paradoxically split second heart sound. The burden on the left ventricle is reflected in the ECG by a pattern of left ventricular hypertrophy and strain, and radiologically by a fullness of the outline of the left ventricle.

Congestive cardiomyopathy presents with a large heart, murmurs of either mitral insufficiency or tricuspid insufficiency and arrhythmias. Such conditions as viral myocarditis fall into this category. In the restrictive form of cardiomyopathy the presenting picture is one of a small heart, no murmurs and few arrhythmias. In this group are found such infiltrative lesions as amyloidosis, scleroderma, glycogen storage disease, gargoy-

lism and ventricular tumors. Both the congestive and restrictive forms present with congestive heart failure, arrythmias and systemic emboli. It is probable that the restrictive form of cardiomyopathy is the most likely here. Definitive tests such as rectal biopsy for amyloidosis or radiological evidence of a tumor can aid in pinpointing the exact etiological agent. However, other systemic manifestations of the infiltrative lesions would commonly be present.

DIAGNOSIS

1) Restrictive cardiomyopathy

2) Pericarditis or pericardial effusion

POST MORTEM FINDINGS

Gross

At autopsy, the patient was found to have a heart of normal colour throughout, but stiff and non-compliant. There was cardiomegaly (wt. 550 gm.) with right and left ventricular hypertrophy. The right ventricle showed some dilatation. All valves appeared grossly normal and no areas of myocardial fibrosis were seen. The right coronary arterial system was predominant. Mild atherosclerosis was present with no localized areas of narrowing or occlusion. There was a moderate degree of atherosclerosis of the aorta particularly in the abdominal portion; a few foci of calcification were noted. All tributaries were patent and free of atheroma. Grossly the pulmonary arteries and lungs were normal; both pleural cavities contained 450-500 cc. of amber coloured fluid. The peritoneal cavity contained 125 cc. of amber fluid. No adhesions were present. The liver was of normal consistency, enlarged (1825 gm.) and on the capsular and cut surfaces showed a typical "nutmeg" appearance. The spleen was hard and waxy to the touch. Thin sections were slightly translucent—no focal lesions were seen.

Microscopic

Heart: The right ventricle, left ventricle and interventricular septum showed extensive deposition of amyloid between myocardial fibres, causing atrophy of the intervening fibres. There was also amyloid in the walls of coronary blood vessels.

Lung: The pulmonary vessels showed a minimal amount of amyloid in their walls. The parenchyma showed small amounts of amyloid in alveolar septa.

Liver: There was mild centrilobular congestion. Amyloid was found extensively in the walls of the portal vein branches in the portal triads; some amyloid was found in the sinusoidal walls.

Spleen: The spleen showed extensive replacement by amyloid.

Kidneys: Both right and left kidneys showed multiple foci of old scarring with lymphocytic infiltration. There were amyloid deposits in vessels and, to a lesser extent, in the glomeruli.

Nervous System: Moderate amyloid deposits were found in the dorsal root ganglia and nerves. Slight deposits were noted in the arterial walls, choroid plexus and sciatic nerve.

Deposition of amyloid was also seen in the thyroid, parathyroid, interlobular connective tissue of the pancreas, adrenals, gingiva, tongue, lamina propria and muscularis of the rectum and in blood vessels of all sizes throughout the body.

ANATOMICAL DIAGNOSIS

1. Primary systemic amyloidosis involving both sides of the heart, spleen, tongue, liver, rectum and blood vessels throughout the body.

2. Congestive heart failure.

DISCUSSION

It has long been recognized that amyloidosis may occur in the absence of any apparent predisposing cause. Once considered a great rarity, this primary form of the disease has been shown to be far commoner than was at one time supposed and is now frequently diagnosed during the lifetime of the patient. The demonstration of amyloid in biopsy material is the most conclusive method of establishing the diagnosis and the value of rectal biopsy has recently been reported. Investigations of a large family by American workers have provided evidence that the disease may occur in a familial form, being transmitted as a Mendelian Dominant characteristic.

With its tendency to involve a wide variety of tissues, it is not surprising that the clinical features of primary amyloidosis are not only varied, but capable of simulating many other diseases. The natural history of the disseminated form however, is generally characterized by a progressive afebrile illness associated with particular signs and symptoms most frequently affecting the cardiovascular and alimentary systems. In the case of the former, intractable cardiac failure may result and this is the most common clinical manifestation. Primary amyloidosis should always be considered when confronted with cardiac failure of uncertain cause.

Amyloid is a hyalin-like material, apparently of protein nature distinguishable from other hyalins by special staining reactions, the site of deposition, and the nature of the conditions in which it occurs. Because it was erroneously considered of starch-like nature, it was originally called amyloid; however, the true chemical nature of amyloid is not known. Variability in staining reaction suggests that amyloid is probably not a single chemical substance but a series of closely related protein compounds. It is grossly a structureless translucent material which transmits the colour of underlying tissues.

Microscopically, it is a hyalin substance which accumulates between parenchymatous cells in connective tissue. Two varieties of amyloidosis are commonly recognized, and are referred to as primary and secondary. Secondary amyloidosis is the most common form and is associated with chronic infections or destructive diseases such as tuberculosis, leprosy, osteomyelitis, leukemia, lymphoma and myeloma. Organs most involved are spleen, liver and adrenals. Blood vessel walls tend to be affected first, and most prominently in these organs. Primary amyloidosis which occurs in the absence of known predisposing disease involves tissues of mesenchymal origin rather than the parenchymatous tissues characteristically involved in secondary amyloidosis. Primary systemic amyloidosis usually affects individuals of middle age or beyond and develops slowly. The muscles of the heart, tongue, gastro-intestinal tract, media of small blood vessels and lungs tend particularly to be affected. Macroglossia and cardiac hypertrophy are quite common manifestations and the myocardial deposit appears to contribute to cardiac failure. The pericardium and epicardium are frequently involved, the involvement being either nodular or diffuse. In the nodular form, deposits may be few or many, and may vary from 1 mm. to 4 cm. in diameter. The nodules are usually pearly-gray and are translucent. In the diffuse type of amyloidosis the epicardium and pericardium are thick, gray-yellow, and semitransparent. Microscopically the blood vessels of the pericardium as well as the interstitial tissues are involved. The myocardium is involved more often than other parts of the heart. Both the atria and ventricles may be either diffusely or focally affected. In diffuse involvement the atrial and ventricular walls are most likely to be thick and leathery. Usually they are firm and pale gray, tan, or brown and have a waxy translucent homogeneous appearance. The muscle cuts with increased resistance and on opening the heart, the chambers do not collapse but retain their globular shape. Microscopically, there are two types of involvement, both of which follow a characteristic pattern. In the first type, amyloid is found in the blood vessels including the main coronary arteries, arterioles, capillaries and veins. In the second type, there is diffuse interstitial infiltration of the myocardium. The myocardial fibers are compressed and undergo necrosis and atrophy, which may be extensive. With excessive deposition the muscle cells can almost completely disappear leaving empty amyloid rings or solid sheets of amyloid. Fragmentation of myocardial fibers is frequent.

Gross infarction of the myocardium may occur as the result of obstruction of a coronary artery by a nodular density of amyloid. Amyloid deposits are commonly present in heart valves but valvular involvement is usually slight and may only be demonstrable in microscopic sections. Signs of cardiac insufficiency are the most important clinical features of primary amyloidosis. The patients are usually 50 yrs. of age or older, usually have not had evidence of previous hypertension and gradually develop cardiac failure and cardiac enlargement. The response to digitalis and other forms of therapy is poor and death occurs several years after the onset of symptoms. When coronary arteries are affected, stenosis or occlusion may result with consequent angina pectoris or myocardial infarction. Secondary hypertrophy of the right heart may occur due to the deposits of amyloid in the pulmonary vessels and the alveolar walls of the lungs. On rare occasions, amyloidosis has been described only in the heart with no other organ involvement. In summary, amyloidosis often involves the heart, and experienced clinicians have learned to suspect this disease in any patient presenting with unexplained cardiac enlargement or refractory congestive cardiac failure. In such a patient with undiagnosed heart disease, amyloid disease should be considered, biopsy material obtained and appropriately stained for definitive diagnosis.

R. D. Nicholson 6T9

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Morris Simmonds - Pioneer Endocrinologist

Endocrinology—This field of medicine is now recognized as a vast area that influences almost every other field of medicine. However, this has not always been the case—in fact it has only been in the last couple of decades that the intricate balance between these glands has been appreciated. Since the early workers in this field lacked the modern tools of physiology and biochemistry, progress was slow. Studies were based mainly on the clinical and pathological pictures that resulted from hypo- or hyper-function of a gland, and it is amazing how accurate their descriptions were of disease entities, in spite of the meagre evidence for them. One such example is that of "Hypophysial Cachexia"—published by a German physician, Morris Simmonds, in 1914—now known as Simmonds' Disease.

Morris Simmonds was born in 1855 on the Danish island of St. Thomas but at the age of six he moved to Germany, where he studied at universities in Tübingen, Leipzig, München and Kiel, graduating in 1879. The young Simmonds continued his studies at Kiel under Heller and Esmarch—a choice which greatly influenced his future direction in medicine. For it was Heller who stimulated his interest in pathology, which eventually led him to describe the disease which now bears his name.

As a young man, Simmonds felt he wanted to be a general practitioner, a field for which he was well suited with his tact, manner and warm-hearted nature. With this in mind, he moved to Hamburg, became an assistant to Bulau and later opened his own practice. But even with the busy life of a G.P., he was drawn back into pathology and anatomy and he continued to study and write papers which were to make his name well-known.

By 1889, Simmonds was a renowned pathologist and so it was no surprise that when Fraenkel left the St. George Prosbduk, Simmonds was named as his successor. In this capacity he continued his work in pathology, even though he had very meagre equipment and was still carrying on his busy general practice. Indeed it seems difficult to understand how a dedicated general practitioner who was so adored by all his patients, could have found time to do such meticulous work.

In 1905, St. George's Hospital opened a new pathology department which had been built with Simmonds' advice and design, and was for many years the most modern department of its kind on the continent. It was built like an operating theatre, incorporating many new techniques for the reduction of infection: steaming of the room every day, no pointed knives, running water beside each stone slab table and the storage of instruments in water-tight cupboards; all of which seems common sense now but was then revolutionary. However, his new responsibilities led to an attrition of his own private practice which he finally gave up in 1909.

With more time, Simmonds engaged in research more vigorously. His original interest had been in the male genitalia but the endocrine glands soon became the target of his investigation. This eventually led to his classic paper in 1914 in which he described the picture of "Hypophysial cachexia":

> A forty-six year old woman was brought in coma to the hospital. Two days prior to admission she had gradually begun to lose consciousness. A careful physical examination revealed little except a very thin, pale female appearing much older than her stated age. She never recovered from the coma and died the day after admission.
>
> At autopsy no abnormalities were found execpt for a very small, soft, pituitary gland, which showed a high degree of atrophy. . . . On further inquiry it was revealed that her symptoms had their onset immediately following severe puerperal sepsis. From that time on, she was very weak, half bed-ridden, unable to work, had attacks of dizziness and loss of

consciousness, and had lost weight and aged quickly. She had been diagnosed as precocious senility—on the basis of her old, tired appearance, wrinkled face, and loss of teeth.

Simmonds emphasized the importance of early senility and the almost total destruction of the pituitary, which are still the basis of the modern diagnosis of Simmonds' disease (some of the other features taken alone have led to erroneous diagnosis of Simmonds' disease). But what is truly remarkable is that Simmonds made his description of the pathological and clinical syndrome over ten years before any modern advances in pituitary physiology occured.

Simmonds was also Secretary of the Pathological Society for many years, and for a long time the President of the Medical Society in Hamburg. When the University of Hamburg was founded he was given an honorary Professorship and took an active part in teaching, despite his advancing years. His personal life was enriched by a very happy marriage, but saddened by the death of his three sons during his lifetime. He was also afflicted with Parkinson's disease, but even though this progressive and fatal condition forced him to give up his post as Prosektor, he never complained.

Morris Simmonds died in September 1925, just after his seventieth birthday. It is hoped that future generations will think of him as a kind-hearted, selfless man who made a foremost contribution to man's fundamental understanding of disease. As Theodor Denek said of him, "Koennen und Goennen"—meaning a man who can do well enough for himself and never begrudges anyone credit for what he has done.

Miss P. Kirkpatrick, B.Sc. 6T9

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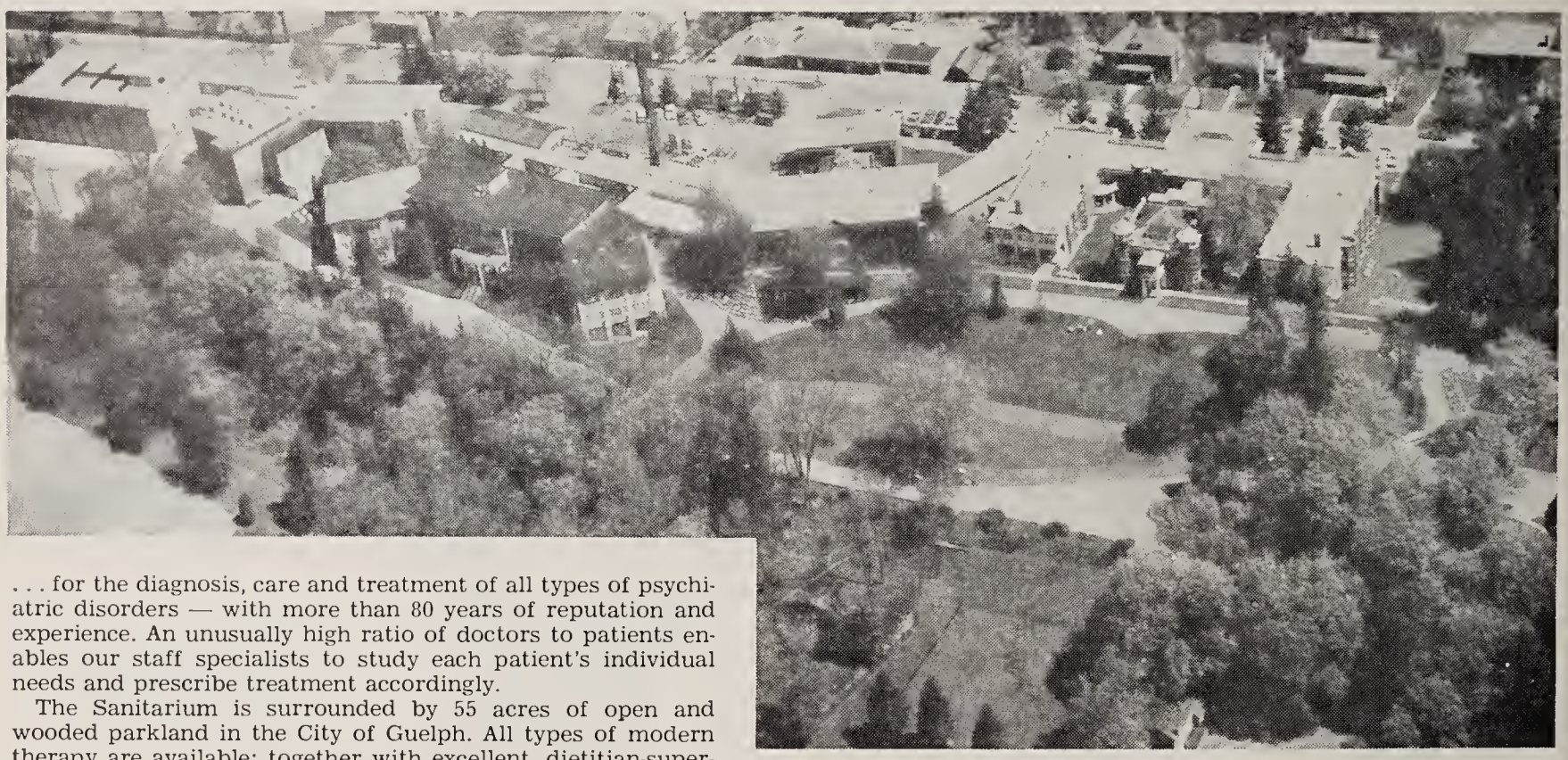

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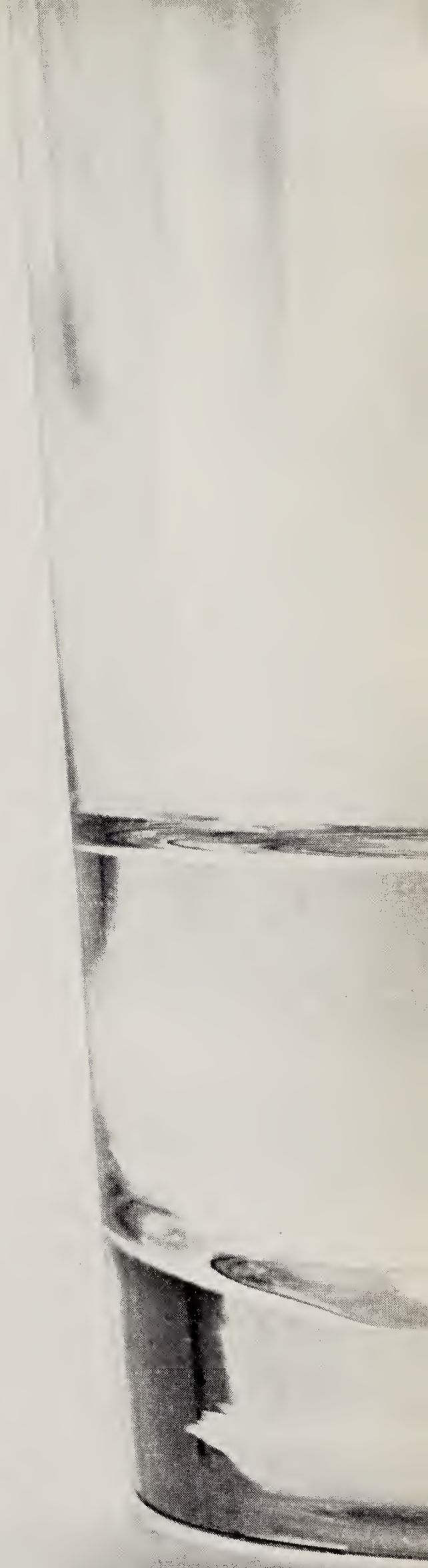

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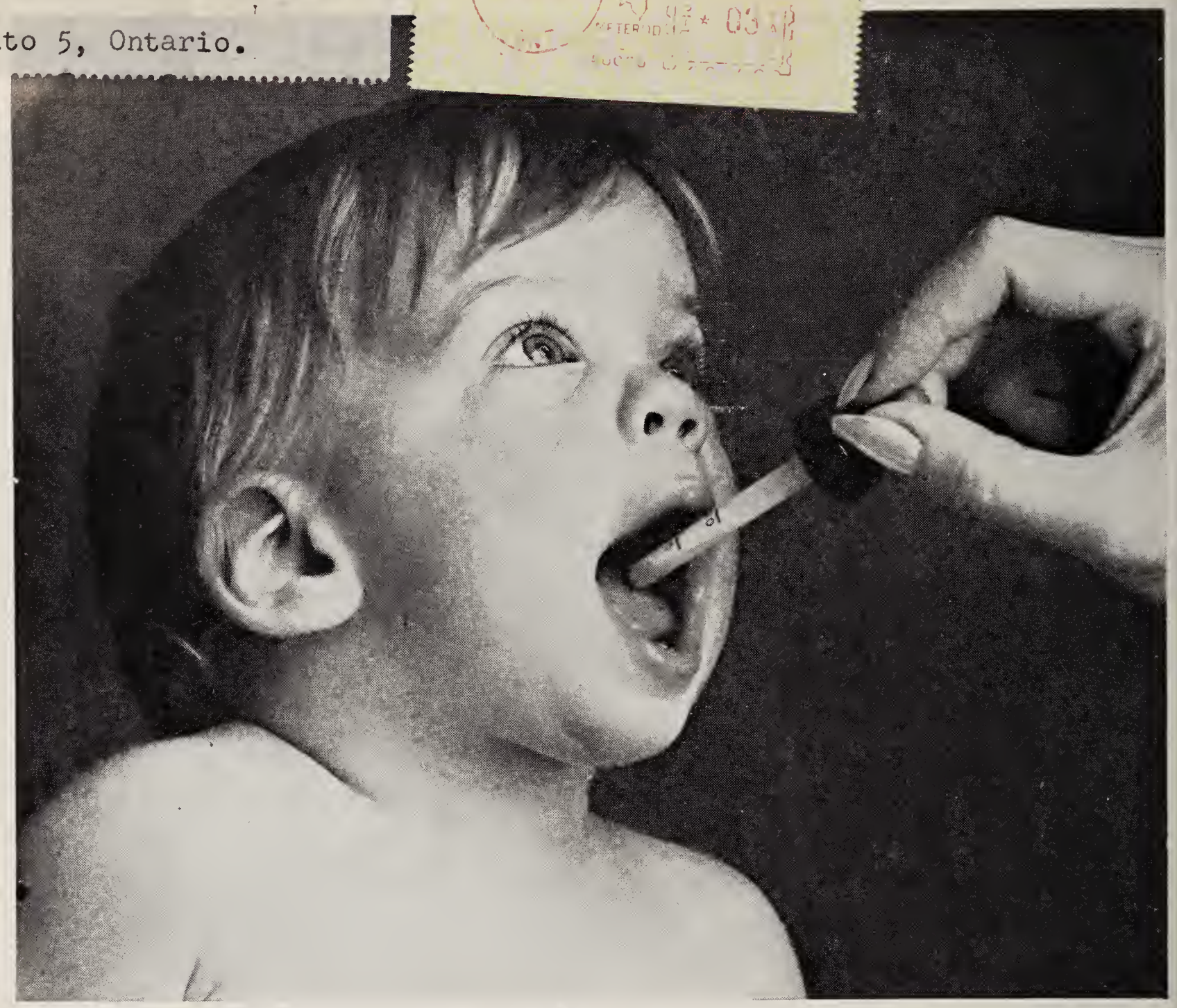

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